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NOBEL PRIZE LECTURES*

INTRODUCTION

THE Nobel Prize in medicine and physiology for 1956 was awarded jointly to Dr. Andre F. Cournand of Columbia University College of Physicians and Surgeons, New York City, Dr. Werner Forssmann of Bad Kreuznach, Germany, and Dr. Dickinson W. Richards of Columbia University College of Physicians and Surgeons, New York City, for their contributions to cardiovascular physiology resulting from the discovery and development of cardiac catheterization. Their Nobel Lectures were delivered at the Caroline Institute, Stockholm, on Dec. 11, 1956. Dr. Forssmann spoke first, presenting the early history of cardiac catheterization, particularly his own experiments. Dr. Richards followed, describing the investigations of Dr. Cournand and himself during the twenty-five years of their joint effort. Dr. Cournand, in the third Lecture, discussed the physiology of the pulmonary circulation.

The Lectures of Dr. Richards and Dr. Cournand are published herewith.

THE CONTRIBUTIONS OF RIGHT HEART CATHETERIZATION TO PHYSIOLOGY AND MEDICINE, WITH SOME OBSERVATIONS ON THE PHYSIOPATHOLOGY OF PULMONARY HEART DISEASE

DICKINSON W. RICHARDS, M.D.

NEW YORK, N. Y.

THE study of the right heart in man has held a continuing place in the researches of Dr. Cournand and myself over the past 25 years, both under physiologic and pathologic conditions. Measurements made in this exact location have provided a key to almost all the syntheses, all the integrations, that we have attempted in elucidating the nature of cardiopulmonary function.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the First Medical Division and the Chest Service, Bellevue Hospital, New York, N. Y.

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In the realm of pathology, pulmonary heart disease also occupies a key position, affected as it is by all manner of pulmonary as well as circulatory dysfunctions. With many of these we are particularly concerned in our research studies of the present day.

Using these two subjects as a central theme, I should like now to give a brief account of our research from its beginning.

The origins of any systematic research are many, extending widely, as well as far back in time. Many also are the supporting and sustaining research activities which are in progress simultaneously. We find ourselves deeply indebted to our colleagues throughout the world, for such assistance over many years. We wish to acknowledge also the institutions which have given us financial support, especially the Commonwealth Fund, the Life Insurance Medical Research Fund, and the United States Public Health Service.

The foundation upon which the research of Dr. Cournand and myself chiefly rests is the work of Lawrence J. Henderson of Harvard. Biochemist, physiologist, natural philosopher, student of Arrhenius, ardent disciple of Claude Bernard, Henderson achieved as his great single contribution the definitive integration of the respiratory function of the blood.[1] But his horizon was far wider than this. He was a general physiologist in the broadest sense. For him the physical chemistry of the blood was but a single link in the whole circulorespiratory synthesis. Such breadth of view was inherent in everything he thought or did, and this could not help but be reflected, in some degree, in those whose good fortune it was to be associated with him. It was from Henderson that we derived the simple but essential concept that lungs, heart, and circulation should be thought of as one single apparatus for the transfer of respiratory gases between outside atmosphere and working tissues.

This concept was of course not new, was in fact in the great tradition of Krogh, of Lindhard,[2] of Liljestrand[3,4] and their collaborators, who, with the methods then available, worked out to a remarkable extent in man the performance of the normal cardiorespiratory apparatus, in rest and exercise. Liljestrand made also a number of studies in disease. In the late nineteen-twenties and early thirties, the active research team at the Harvard Fatigue Laboratory under Henderson continued this exploration of cardiocirculatory patterns,[1] to which their complete studies of the respiratory function of the blood constituted an important contribution.

During all this time, however, and indeed for a total period of nearly 40 years, there was in the study of the heart and circulation in man one measurement or set of measurements which was conspicuously in default, namely, the state of the blood as it enters the right heart, its respiratory gas contents, its pressure relations, and its rate of flow.

While the full potentialities of these measurements were not then appreciated, it was well known that an accurate figure for the respiratory gases in the mixed venous blood would enable, under conditions of a physiologic steady state, a reliable measurement of total blood flow through the lungs. The principle was the simple one originally stated by Fick,[5] that of dividing the arteriovenous difference—the amount of oxygen taken up (or CO_2 given off) by unit volume of

flowing blood—into the total amount of this gas taken up (or given off) by the lungs per minute.

Only those who have worked through all or a part of those times can appreciate how ardently this information was sought after, and by how many devious approaches. The majority of these involved the use of the lungs as a tonometer, equilibrating the oxygen or the CO_2 of the lungs with that of the incoming pulmonary arterial blood. The early experiments of Loewy and von Schrötter,[6] the rebreathing techniques of Plesch,[7] later of Christiansen, Douglas, and Haldane,[8] and of Yandell Henderson[9] were among the more important of these.

I give special emphasis to this in the present account because it was to this long-standing problem that Dr. Cournand and I applied ourselves when we began our work in 1931, on the service of Dr. James Alexander Miller in Bellevue Hospital. There was nothing original in our approach. We simply tried, as others had done before, to establish gaseous equilibrium between lungs and inflowing blood by rebreathing procedures, and to do this especially in patients with chronic pulmonary disease. But as others also had found before us, diseased lungs would not mix air evenly, and after 3 years it became apparent that we had failed completely in these attempts.[10] And yet the failure was not quite complete. There proved to be some highly interesting things about this uneven mixing in diseased lungs. Robert Darling, working with us, extended earlier work in the same field by developing a breath-by-breath analysis of intrapulmonary mixing of inspired air, using the simple method of washing out intrapulmonary nitrogen through inhalation of pure oxygen.[11] This subject has since been further studied by many investigators and it constitutes now an important branch of pulmonary physiology. In our early experiments with Darling, two immediately practical features were worked out: an open circuit method of measuring residual lung volume, and in the same procedure, a rough but useful index of intrapulmonary mixing, namely, the nitrogen remaining in the lungs after oxygen breathing.[12] At this time also, with Eleanor Baldwin we were developing other practical methods of measuring pulmonary functions, greatly aided here by similar work in progress elsewhere, especially in the clinic of Knipping and Anthony in Hamburg.[13,14] By the late nineteen-thirties, we were able to describe the ventilatory functions of the lungs, and, with pulmonary measurements supplemented by arterial blood studies in rest and exercise, define to some extent the mixing and the diffusional aspects of pulmonary alveolar or alveolar-capillary functions.[15] But we still could not measure blood flow through the lungs, and could not, therefore, move into those broader concepts of cardiopulmonary function which now began to be our goal.

We were aware of the earlier experiment of Forssmann,[16] and had followed closely its isolated uses in Germany, Portugal, South America, and France. Late in 1940, Cournand and Ranges[17] took up the catheterization technique, showing in their initial studies that consistent values for blood gases could be obtained from the right atrium, that, with this, cardiac output could be reliably and fairly accurately determined by the Fick principle, and that furthermore the catheter could be left in place for considerable periods without harm. Not long after,

through the interest of Homer Smith, and with the assistance of Bradley, pressure recordings by a Hamilton manometer were added to the other techniques. Blood volumes by Gregersen's method were also included.[18]

By this time, therefore, after 10 years of work, we had assembled a fairly comprehensive group of methods for the analysis of cardiopulmonary function, methods which could be applied not only to normal man but to patients in even the most severe and acute stages of decompensation.

The stage was now set for the study of cardiac and pulmonary functions in many forms of clinical disease.

First to be undertaken was an investigation of traumatic shock in man.[18,19] The United States was by this time at war, and further information on the hemodynamics of shock, quantitative measurements of this, and of the effects of treatment were urgently needed. These studies proceeded quite rapidly. It was demonstrated: that with a deficit of 40 to 50 per cent in blood volume, there were critical depressions in cardiac output and in return of blood to the right heart, worsening as shock continued unrelieved; that peripheral resistance tended to be maintained in hemorrhage and skeletal trauma, and greatly increased in severe burns; that an important corollary of this was reduced peripheral blood flow, demonstrated particularly in the case of the kidneys; that whole blood offered great advantages over plasma as sustaining therapy. Other forms of treatment were evaluated. Vasomotor factors, problems of so-called irreversible shock were approached but not solved. In certain cases of severe burn, the catheter was left in place for more than 24 hours, to provide a means of intravenous treatment, with no harm resulting, a further indication of the safety of the procedure.

Even during these war years a number of basic contributions were made, such as the advancing of the catheter, first into the right ventricle, and then into the pulmonary artery, enabling new measurements, some of them as important physiologically as the original right atrial.[20] In the field of clinical heart disease, cases of heart failure with high cardiac output were identified and differentiated from "low output" failures.[21] McMichael and Sharpey-Schafer[22] in London had made similar observations independently. Baldwin[23] studied a case of congenital heart disease with interventricular septal defect. There were numerous improvements in technique.

With the cessation of hostilities in 1945, we were free to look more broadly at problems of disease. By this time others were at work with the same procedures, in various parts of the world.

The application of cardiac catheterization to the diagnosis of congenital heart lesions was an obvious one, and a number of investigators became interested and pursued this inquiry with great skill. The early studies of Cournand, Janet Baldwin, and Himmelstein[24] were extended by much additional work by Bing,[25] Dexter,[26] and others. It should be noted that the great advance represented by the surgery of congenital heart disease, under such men as Gross,[27] Blalock,[28] Crafoord,[29] and Brock,[30] was under way before cardiac catheterization, and has moved fundamentally on its own. The cardiac catheter has been, however, a primary aid. Sharing with angiocardiography the ability to define the anatomic lesions, the catheter also quantitates the volumes and pressures of abnormal flow,

thus defining for the surgeon both the nature and extent of the disorder. By repeated catheterization can be determined postoperatively the degree to which a normal circulation has been restored.

The measurements now available were adequate for a more general study of the physiology of heart failure, particularly since these could be carried out under conditions of cardiac decompensation and again following recovery. Pressures and flow in the pulmonary circulation gave an index of performance of the left ventricle; the same measurements in right heart and great veins, an index of performance of the right ventricle. Many forms and degrees of failure were defined, and their responses to treatment measured: limited or fixed cardiac output, not responding to exercise; left ventricular failure with pulmonary hypertension; right ventricular failure with systemic venous hypertension; the congestive state with high blood flow, and with low; very low cardiac output without congestion; the dynamic effects of cardiac arrhythmias; the circulation in constrictive pericarditis.[31,32] The congestive state as such was established as a dominant aspect of heart failure, regardless of the level of general or regional blood flow.

An important contribution, in its therapeutic as well as its physiologic implications, was the analysis of the action of the digitalis glucosides, by Ferrer and Harvey in our laboratory,[33] and also by McMichael and Sharpey-Schafer,[22] by Bloomfield,[34] and others. It was established that digitalis acts favorably only upon ventricles overdilated, with excessive filling pressures and inadequate emptying; that in such hearts it acts rapidly to increase the energy of contraction, increase stroke volume, and promote adequate emptying, thus relieving the congestive state; that it performs with regular as well as irregular cardiac rhythms.

This large body of new knowledge of the dynamics of the circulation inevitably brought again under critical review the original Starling principle,[35] namely, that the energy of ventricular contraction is proportional to fiber length, that is, to diastolic ventricular volume, and that this relation holds up to a certain optimal fiber length, beyond which myocardial contraction progressively fails. Alternatively, in clinical studies, the more readily measured diastolic filling pressure has been commonly used, instead of diastolic volume, a relationship developed before Starling, by Otto Frank. In this general inquiry, contrary to the usual sequence, it was the clinical physiologists who stimulated the general physiologists to further research,[36] and additional work in animals, especially by Hamilton,[37] by Rushmer,[38] and others, has added much interesting material. Many questions are still in controversy, but there would appear to be fairly general agreement that in the normal heart under stress, the basic Starling relation is overridden by other influences, such as sympathetic control of muscle tone, the heart in exercise increasing its emptying rather than its filling volume; but that in the failing heart the fundamental relation between fiber length and energy of contraction may again emerge.

One particular form of acquired heart disease that has come under intensive study in the last 6 years is, of course, mitral stenosis. The magnificent achievement of cardiac surgeons in the partial or complete relief of this mechanical block has permitted also the comparative study of the hemodynamics of the circulation

before and after this surgical procedure. Many factors are involved in the selection of patients for surgery.[39] By and large, clinical improvement postoperatively has coincided with fall in pulmonary arterial pressures, and frequently with increase in resting or in exercise cardiac output. The total physiologic readjustment, however, is a complex one, and the interrelations between cardiac output, pulmonary and systemic pressures, and ventilatory and other pulmonary functions have not yet been fully worked out. Among the many important contributors in this field, Ellis,[40] Werkö,[41] Dexter, Soulié, Donald, and Lequime may be mentioned.

The further extensions of the catheterization technique that are now being made, exploring the left atrium, the left ventricle, and the systemic aorta, are beyond the scope of the present discussion.

These numerous excursions into cardiac physiology, which I have just reviewed, have indeed been a major feature of our work, and yet they somewhat obscure the fact that Dr. Cournand and I have from the beginning thought of ourselves as primarily pulmonary rather than cardiac physiologists. I should like to outline now, though in the briefest possible terms, some of the aspects of clinical pulmonary physiology that also have been under study in our laboratory during the past several years.

I return for a moment to the work of our former colleague, the late Dr. Eleanor Baldwin, and in doing so wish to pay tribute to her for the vital part that she played in our whole research achievement. With the group of standard methods that I referred to earlier, she studied over a period of 10 years a large number and variety of cases of chronic pulmonary disease. Inclusion of circulatory data from cardiac catheterization in many of these patients completed the picture of cardiorespiratory failure. It was found that these cases on analysis fitted well into the broad categories of pulmonary insufficiency that we had described earlier: the gross ventilatory, with restrictive or obstructive aspects, and the alveolar-capillary, with primary disturbances in respiratory gas exchange. Some disorders, such as pulmonary emphysema, were complex with various combinations of these factors. One definitely new physiologic group emerged, that of the diffusional insufficiency or alveolar-capillary block, with the major interference at the alveolar-capillary interface.[42]

This type of broad physiologic analysis, with subsequent therapy directed to precise and specific aspects of insufficiency, has proved to be of great value in the clinical management of this large category of chronic disease.

In the past decade there has developed a much more exact analysis of intrinsic pulmonary function, to which I can refer here only briefly and inadequately. It is a development, however, which constitutes one of the most significant advances in basic physiology that have been made in the various fields to which cardiac catheterization has contributed. The general subject is that of diffusion of gases across the alveolar-capillary membrane and of the ventilation-perfusion relationships in the lungs. Two independent groups of investigators have been largely responsible for this development. At the University of Rochester, Rahn and Fenn[43] approached the subject initially by way of a description of the various possible relationships between oxygen uptake and CO_2 elimination

in the lungs: the respiratory exchange ratio. The other group, consisting first of Riley and Lilienthal, and later of Riley, Cournand, Donald, and associates,[44,45] developed first a simple formula for the determination of mean alveolar oxygen tension, then proceeded to study the special properties of the oxygen dissociation curves of blood. Using the principle that at high oxygenation equilibrium of oxygen between air and blood is complete, whereas at low oxygenations there is a distinct alveolar-capillary oxygen gradient, they found it feasible to use high and low oxygenations in human subjects to measure the diffusion process. Extension of the work led to a general definition of ventilation-perfusion relationships, separating effective "alveolar" ventilation from ineffective "dead space" ventilation, on the one hand; and effective "alveolar" perfusion from ineffective "venous admixture," on the other. Developments in this field, under Riley, Comroe and Forster, Rossier, and others, cannot be reviewed further here.

The discussion up to this point has been indeed an overlong introduction to the problem of pulmonary heart disease. Yet this information is not irrelevant. The heart in chronic pulmonary disease is at a crossroads, itself a consequence of both pulmonary and cardiocirculatory disturbances.

Pulmonary heart disease, or *cor pulmonale*—cardiac hypertrophy and dilatation secondary to disease of the lungs—was clearly delineated by Laennec nearly 150 years ago, but has attracted considerable attention only within the past generation. Its importance and its incidence are increasing, in large part because patients with chronic pulmonary disease now live longer, being protected somewhat from infection, and relieved and sustained, in some instances for considerable periods, by symptomatic therapy.

At the present time, a very considerable proportion of patients suffering from chronic pulmonary disease with progressing pulmonary insufficiency will eventually develop cor pulmonale. In some instances the heart failure becomes chronic and continues for years; in others it appears only terminally; in still others there may be repeated episodes of right heart strain and failure, especially during recurring pulmonary infection. These clinical patterns are only now beginning to be defined, as the cases are followed over many years; as yet, a generally accepted classification of pulmonary heart disease has not been made. In the present brief sketch I shall move rapidly through some of the more frequently encountered forms, their natural history and physiologic components. This description is based chiefly on the work of Harvey and Ferrer[46] in our laboratory.

It will be convenient to use as a prototype chronic diffuse pulmonary emphysema, concentrating on the features concerned with the flow of blood through the lungs and the action of the right heart.

The principal factors inducing right ventricular strain, hypertrophy, and failure can be stated very simply: (1) pulmonary hypertension, from one cause or another; and (2) secondary influences throwing a burden on the right heart, such as anoxia, increased blood volume, polycythemia, increased cardiac output, disordered breathing mechanics.

The division of pulmonary emphysema, as originally made by Baldwin and associates,[42] into 4 physiologic groups, is applicable also to a consideration of cor pulmonale. We shall assume here the most common pathogenetic form of emphy-

sema, that proceeding from chronic bronchitis and bronchial obstruction, moving on to the hyperinflated obstructive type of ventilatory insufficiency.

In the first and mildest of these groups, the disturbances of pulmonary mechanics are not associated with arterial hypoxia or difficulties with CO_2 elimination. In these cases pulmonary vascular pressures are within normal limits and there is no significant right heart strain.[20]

In the second group, ventilatory function is more severely curtailed, often to one fourth or one fifth of normal, and anoxia appears. Work or effort of breathing is much increased. Carbon dioxide elimination is still adequate. It is extraordinary in some cases how much destruction of pulmonary tissue can exist, how little the remaining effective diffusing area, with the lungs still able to carry on CO_2 exchange. Similarly, pulmonary arterial pressures can remain normal, at least during rest, with a remarkably small proportion of available vascular channels. In general, pulmonary arterial pressures seem to rise roughly in proportion to the degree of arterial hypoxia.[31] That this is due in large part to the constricting effect of anoxia upon the pulmonary vascular apparatus is suggested by the fact that physiologically this hypertension is usually reversible when the patient's compensation has been restored, and the anoxic state relieved. On the negative side, we have found not too clear a correlation between the degree of pulmonary hypertension, and the extent of anatomic pulmonary vascular change, either muscular hypertrophy or arteriosclerosis.

Clinically, the right heart often begins to show objective evidence of hypertrophy and dilatation when pulmonary arterial pressures exceed twice normal values.

In the next or third group, anoxia is more profound and CO_2 retention with hypercapnia is added. The aeration of the alveolar spaces has entered its final stage of decompensation, and the full state of alveolar hypoventilation is established. Here the primary constricting effects of anoxia send the pulmonary arterial pressures to higher levels; and secondary effects of both anoxia and hypercapnia place their added burdens on the heart.

The extent of the breakdown, actually of reversal of supposedly homeostatic mechanisms, is remarkable. Profound arterial oxygen unsaturation leads to marked polycythemia, total blood volume increasing by the amount of the increased red cell mass. This overfills the blood bed, including the heart, and drives the heart, so to speak, to increased output and eventual failure. The pulmonary vascular channels also may be congested, with further anoxia resulting. That this is not a favorable homeostasis, but an unfavorable excess response, can be shown directly by a phlebotomy, which often brings immediate and striking improvement in all functions.

Even more widespread are the systemic effects of elevated CO_2. The rise in alveolar and blood CO_2 tensions produces at the kidneys, as shown by the work of Pitts[47] and Gilman,[48] a retention of bicarbonate, thus further raising blood and tissue CO_2 levels, though of course relieving in part the uncompensated gaseous acidosis. Continued high pCO_2 apparently depresses the sensitivity of the respiratory center to the CO_2 stimulus, although there has arisen recently some question regarding this effect.

What further effects the retained bicarbonate may have on electrolyte and water balances in the body is not known.

Most extreme of the forms of physiologic dysfunction in emphysema are those rather uncommon cases of severe alveolar hypoventilation, sometimes called the Ayerza syndrome, in which all of the above-mentioned trends are manifested to maximum degree, and yet sometimes with only mild anatomic changes in the lungs.[42] Functionally, however, there is always bronchial obstruction, marked alveolar hypoventilation,[49] and the most severe ventilation-perfusion disturbances. Even in these cases the entire circulation can often be restored to normal, with normal pulmonary arterial pressures and cardiac output reduced to normal values, by vigorous symptomatic therapy, relieving the bronchial obstruction, the hypoxia, hypercapnia, polycythemia, and hypervolemia, and by active treatment of congestive failure.

There are other forms of pulmonary disease in which cor pulmonale is a significant complication. There is a category, for example, in which there has been a progressive loss of function or a destruction of total pulmonary tissue, down to a critical level, to an irreducible minimum. Cor pulmonale with failure may develop in such cases, usually terminally or as a very late stage.[50] Such cases include those of severe kyphoscoliosis, occasionally widespread and far advanced pulmonary tuberculosis, some cases of bullous emphysema with replacement or compression of active lung tissue. I mentioned earlier another newly-defined form of pulmonary dysfunction, that of diffusion insufficiency or alveolar-capillary block. Such cases, in the advanced stages with continuous hypoxia, commonly have right-sided heart failure as a late complication. Still another important type is that of primary pulmonary vascular narrowing, represented by multiple pulmonary embolization, pulmonary schistosomiasis, and the somewhat controversial entity called primary pulmonary hypertension. In these the right heart strain is directly proportional to pulmonary hypertension, and the patients go eventually into massive right heart failure with low and diminishing cardiac output.[49]

I have dealt with this particular subject, pulmonary heart disease, in somewhat greater detail than the rest of my account, partly to show the type of functional analysis that can readily be made in clinical cases, but partly also to illustrate, what is perhaps obvious, that such analysis is at best superficial, does no more at the present time than set forth what some of the more fundamental problems are.

It is no part of a survey such as this to predict the future, but I should like to mention a few of the areas in which we believe that further basic research might well be concentrated. One important field is the pharmacodynamics of the lung, and especially of the pulmonary circulation. Another that interests me greatly would be an effort to bring together function and structure, a re-examination of pulmonary anatomy by pathologists who are aware of functions and dysfunctions. May it not be possible to obtain, by such collaborative effort, more fundamental evidence on pathogenesis in such presently obscure and yet devastating conditions as pulmonary fibrosis in its many forms, the emphysematous change, bulla formation, the many-sided problem of pulmonary vascular change, the disorders of

the bronchial circulation? Fortunately, work is already under way on many of these problems, by a new and dynamically-minded generation of pathologists. So also with many of the other problems that I have touched upon, in renal and electrolyte physiology, as related to pulmonary disease, in blood formation, the physiology of the respiratory center, and so on.

Summarizing, I have endeavored to present in this review a brief account of the development of cardiac catheterization in our hands, and some of the adventures that we have had with it. These have carried the work into many aspects of cardiopulmonary physiology and pathology. Our findings have been for the most part preliminary, revealing new problems more often than solving old ones. Of great value has been the interest which has been aroused and the excellent new work that has been stimulated in many laboratories and clinics in many countries.

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PULMONARY CIRCULATION. ITS CONTROL IN MAN, WITH SOME REMARKS ON METHODOLOGY

ANDRE F. COURNAND, M.D.

NEW YORK, N. Y.

THE development of our knowledge of the pulmonary circulation in normal man has followed the introduction of the cardiac catheter in clinical investigation. In 1941, this new tool was only the key in the lock—although this is in no way a minimizing of Dr. Forssmann's brilliant and courageous experiment. To guide our hand in turning this key, we had all the knowledge accumulated through the years by physiologists in their studies of animals; and to one, Dr. William F. Hamilton, I owe a more personal debt of gratitude for his constant advice and kind criticism. Basically our difficulties were then, as they are still, those of measuring pulmonary blood flow, pressures, and volume. And, since the reliability of experimental data is no better than the reliability of the measuring techniques employed, I should like, before discussing our present understanding of the pulmonary circulation, to consider briefly the limitations of our methods.

LIMITATIONS OF THE METHODS OF MEASUREMENT

1. *Pulmonary Blood Flow.*—As D. W. Richards has pointed out in his lecture, the measurement of pulmonary blood flow in man did not appear at first to pose an important problem, once catheterization of the pulmonary artery, cannulation of a peripheral artery, and spirometry had supplied the data necessary to apply the principle described by Fick in 1870. But the application of the Fick principle involves more than the simple substitution of analytical values into a ready-made equation, and the problem which had to be solved is an illustration of the caution necessary when physical principles are applied to biologic measurements.[1,2,3,4,5]

The Fick principle can be used to measure flow in a physical system in which a stream of constant velocity enters a chamber of constant volume, the volume being sufficiently small so that an indicator substance continually added to the chamber is instantaneously mixed with the volume therein. Then, if the rate at which the indicator enters the chamber is measured, and if the difference in concentration of the indicator in the fluid entering and leaving the chamber is determined, flow can be calculated by dividing the volume of indicator added per unit of time by the volume of indicator gained per unit of fluid flow.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the First Medical Division and the Chest Service, Bellevue Hospital, New York, N. Y.

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But these conditions are not realized in the body, since pulmonary blood flow is pulsatile, and since the rate of transfer of oxygen, the indicator substance, into the pulmonary capillaries is influenced by the cyclic character of ventilation, and may be measured only at the mouth rather than at the alveolo-capillary membrane. Furthermore, blood samples required for the determination of the oxygen content of the blood entering and leaving the lungs are integrated in respect to time rather than in respect to volume; in addition, they must be collected for a finite period instead of from instant to instant, as would be necessary in order to make a continuous measurement of flow.

However, as a result of extensive investigations in animal and in man, it would appear that these theoretical considerations do not introduce an error of large magnitude in the measurement of pulmonary blood flow, provided certain criteria regarding the maintenance of a steady state of ventilation, circulation, and gas exchange are met. Thus, the problems of periodic variations in flow velocity and of arteriovenous oxygen difference, and the matter of time-integrated rather than volume-integrated samples, do not affect the measurement of flow except under the most extreme circumstances. It was pertinent to the solution of this question to demonstrate that the volume of flow measured by the dye-dilution technique, which involves a different principle, agrees rather closely, under a wide variety of conditions, with that obtained by application of the Fick principle.[6,7,8]

2. *Pulmonary Blood Pressures.*—In the early days, pressures in the heart and in the pulmonary artery were recorded[9,10,11] through a single-lumen catheter, connected to a Hamilton manometer, a coupling which raised important technical questions. Whereas in animals it had been possible to limit the distance between the heart and the manometer to the length of a short metal needle, the use of a catheter interposed a column of fluid at least 100 cm. long between the pressure to be measured and the pressure-measuring device. Moreover, the fluid was contained inside a tube, the stiffness of which was considerably less that that of metal; this is an important consideration in view of the fact that the fidelity of a recording system is a function of the stiffness of its parts. It was necessary, therefore, to construct a catheter in which a compromise was made; the catheter had to be sufficiently stiff to transmit pressures accurately, but not so stiff that its introduction into the heart would be dangerous. In addition, damping had to be considered because of the low natural frequency of the system, and because of the need to minimize the artifacts imposed by the mechanical impact of the beating heart (Fig. 1). In general, the proper degree of damping is best determined empirically, as it varies with heart rate, height of pressure, and the location of the tip of the catheter. Indeed, the use of the catheter system for recording pressures within the heart and the thoracic vessels emerges as an art as much as a science. An important progress in technique was the development of a double-lumen catheter through which simultaneous pressures in two contiguous heart chambers and large vessels could be recorded.

The first two tracings of blood pressure pulses recorded simultaneously within the right ventricle and the pulmonary artery are presented here (Fig. 2). They served to illustrate a paper published in 1945,[12] in collaboration with Henry Lauson and Richard Bloomfield, on the use and advantages of this newly-designed double-lumen catheter. For me, this tracing has a special significance,

for it is the first demonstration that the tip of a catheter was placed in the pulmonary artery of man in order to record pressure pulses. Subsequent progress in our knowledge of the dynamics of the pulmonary circulation in man[13] is due in large part to the technique of catheterization of the the pulmonary artery. The part played by Lewis Dexter and his associates in this latter technical development deserves special mention.[14]

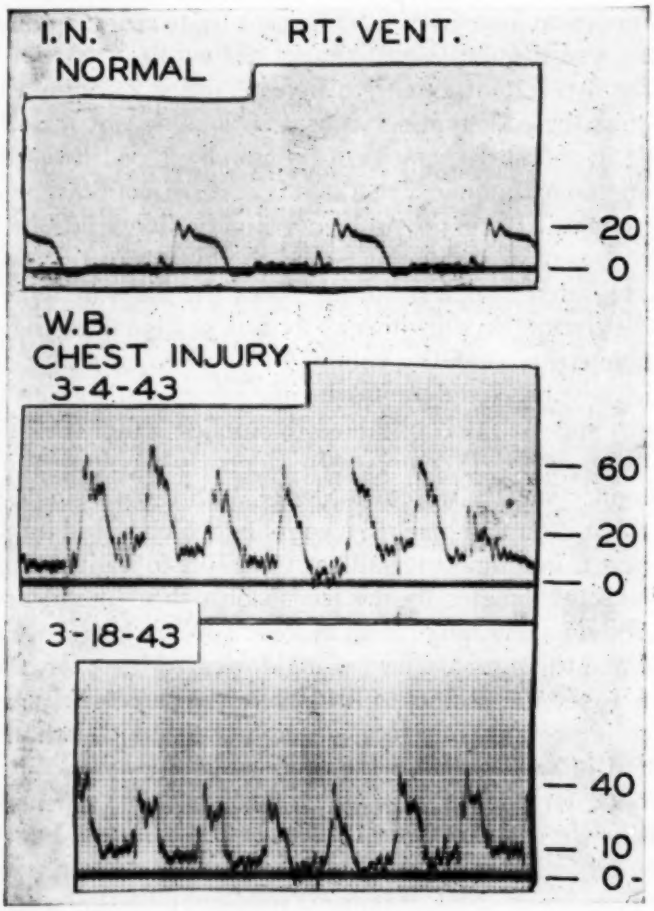

Fig. 1.—Photographic reproduction of the first reported pressure pulses recorded in the right ventricle of a normal man and of a patient with severe traumatic chest injury. (Chart 13 in Ref. 9.) These tracings were obtained through a catheter attached to a Hamilton manometer; they are undamped; the coarse vibrations are due to impacts upon the catheter. The scale is in mm. Hg.

Apart from our efforts to develop a satisfactory catheter, considerable attention was also required for proper operation of the Hamilton manometer. Stanley Bradley, who was assigned by Homer Smith to the team studying shock at Bellevue Hospital during the years of World War II, was initially in charge of this delicate and essential function. Although the Hamilton manometer was subsequently replaced by strain gauges in association with electronic recorders, it is well to recall that most of our early knowledge of pressure pulses was obtained by using this device.

During the past few years recording machines have become increasingly complex and useful, but no matter how sensitive the manometer employed may be, the catheter system itself still remains the limiting factor in the faithful reproduction of human pulse pressures, under all circumstances.

An estimation of the pressure drop across the entire pulmonary vascular system had been of particular concern to physiologists interested in the dynamics of the pulmonary circulation. Catheterization of the pulmonary artery supplied the necessary data concerning pressures at the origin of the system; but the pressure at the end of the system, that is, in the left atrium, although predictable from the diastolic pressure in the pulmonary artery of the normal subject, could not be determined accurately.

A first step in the proper direction was made when pressures were recorded from the left atrium and large pulmonary veins in human subjects under the abnormal conditions provided by interatrial septal defects[15]; however, it was not until very recently that, by means of needles, direct measurement of the left atrial pressure in intact man has been secured. Prior to the latest development, an ingenious indirect method for making this measurement had been developed separately, in 1949, by Hellems and Dexter,[16] and by Lagerlöf and Werkö.[17] It consisted in advancing a cardiac catheter into a peripheral branch of the pulmonary artery until it was firmly wedged.

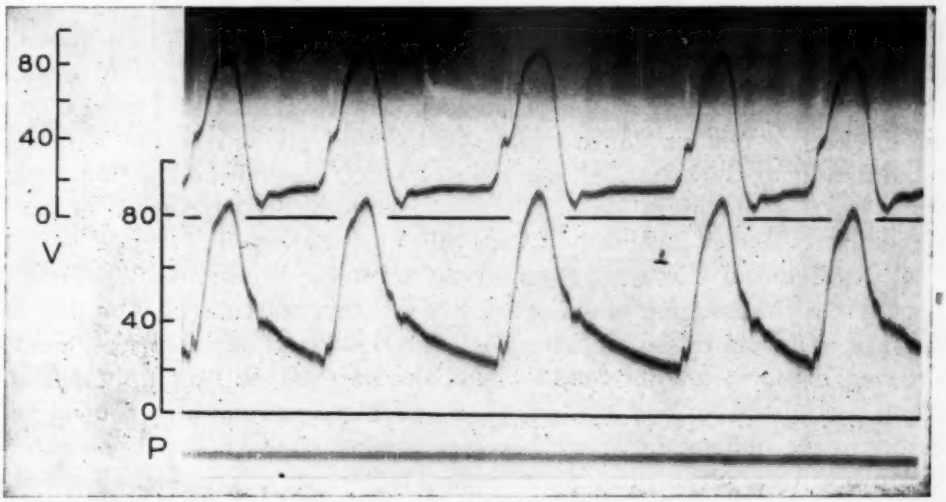

Fig. 2.—Photographic reproduction of the first reported pressure pulses recorded in the pulmonary artery of man.[12] The simultaneous tracings in the pulmonary artery and the right ventricle were obtained through a double-lumen catheter attached to the Hamilton manometer in a patient with severe pulmonary hypertension. The scale is in mm. Hg.

At first it was assumed that the recorded pressure was that in the first freely anastomosing segment of the pulmonary vascular bed distal to the point of wedging, i.e., the capillary bed. Theoretical considerations suggest, and recent comparisons indicate, that the pulse contour and the mean pressures recorded after wedging correspond with those obtained from the left atrium, particularly in subjects with pulmonary venous congestion. This pressure, therefore, can be used, with caution, to derive a fairly accurate figure for the pressure drop across

the entire vascular bed, particularly in cases where vascular pressures throughout the pulmonary circuit are elevated.

3. *Pulmonary Blood Volume.*—Since the pulmonary circulation constitutes a distensible reservoir interposed between the right and the left ventricle, measurements of pulmonary blood volume and of its variations under various physiologic conditions has attracted the interest of clinical investigators. The use of the dye-dilution technique, referred to above, provides an indirect means of measuring this volume, according to a principle first correctly stated and then experimentally established by Hamilton and his school. However, the "central blood volume" thus measured has somewhat vague limits, and it includes the volume in the left heart and that in a large part of the arterial tree. Furthermore, the error of the technique is of the order of 15 per cent of the volume measured; hence, variations of volume amounting to from 150 to 200 ml. may not be significant.

Concluding this long preamble on methodology, I shall now turn to the main theme of my lecture: the control of the pulmonary circulation in man.

CONTROL OF THE NORMAL PULMONARY CIRCULATION IN MAN

From the large body of previous work in animals, particularly in dogs, it was already evident at the inception of our investigation that the relationship between pressure and flow in the pulmonary circulation is quite different from that in the systemic circuit. Although the stroke output of each ventricle is approximately the same, except for temporary differences, the mean pressure in the aorta is 6 times that in the pulmonary artery. This is an expression of a much higher viscous resistance to flow in the systemic circulation, a resistance located mainly at the arterioles, the walls of which are endowed with a thick and circular layer of smooth muscles. By contrast the walls of the small branches of the pulmonary artery have only a very thin muscular media.

1. *Mechanical Factors.*—From these anatomic observations, it might be expected that the influence of the activity of this thin muscular coat on the viscous resistance to flow in the small pulmonary arteries would be a relatively weak one. Moreover, if the vasomotor tone is weak, the part played by purely mechanical factors, such as variations in blood flow and blood volumes, in controlling the pressure in the pulmonary artery becomes proportionally more important.

However, the effects of such mechanical factors are not simple. For instance, if the resistance to flow in the pulmonary vessels remained constant, then the pulmonary arterial pressure would be directly influenced by variations in flow and by variations in left atrial pressure. Since, however, the whole vascular system is distensible, the resistance in the circuit is itself dependent on variations in distending pressure. Thus, an increased flow, or an increased left atrial pressure, will by itself increase the distending pressures in the various pulmonary vessels, open up new channels, thus changing the geometry of the system and thereby lowering the pulmonary vascular resistances. From this it follows that the relationships between pressure and flow in the pulmonary circulation should not be expected to be rectilinear.

Indeed, it was soon apparent, from our studies, that there was not a linear

relationship. For example, measurements made before and after pneumonectomy showed that the pressure in the pulmonary artery rose very little when the entire output of the right ventricle flowed through one single normal lung.[18] Hence, the vascular resistance is strikingly dependent on the rate of flow, and the pulmonary vessels appear to be remarkably distensible within this range. Further support of this observation is provided by the relatively small rise in the pulmonary arterial pressure which is associated with a large increase in pulmonary blood flow observed during exercise in normal subjects and in patients with large left-to-right intracardiac shunts.

Beyond a certain point, however, increases in pulmonary blood flow cause greater increments in pulmonary arterial pressure, and this is presumably an indication of the shape of the curves which relate distending pressure to cross-sectional areas in the pulmonary vessels. In this respect it is interesting to recall that Lilienthal and Riley[19] recently called attention to the relationship existing between the critical level at which pressure in the pulmonary artery increases significantly and the maximum oxygen diffusing capacity, a function closely related to the size of the total alveolo-capillary interface.

Our experiments on the effects of the normal respiratory cycle, positive pressure breathing, and the Valsalva maneuver[20,21,22] showed also the mechanical results of altering the effective, or net distending, pressure in the pulmonary vessels. In addition, they revealed that the hemodynamic situation is further complicated by differential changes in the filling pressure and thereby in the stroke output of each ventricle. These results directed our attention to the important notion of heterodynamism of both ventricles, particularly fruitful in the understanding of isolated ventricular failure.

2. *Vasomotor Factors.*—Since remarkably wide variations in vascular resistance can normally occur in a purely passive fashion, the task of demonstrating the active part that the smooth muscles in the wall of the small vessels may play in its alterations becomes very difficult. Nevertheless, we have knowledge of two agents which appear to affect the resistance to flow in the pulmonary circulation by modifying the muscular tone of its vessels. These two agents are hypoxia and acetylcholine.

a. *Hypoxia:* Our interest in hypoxia was stimulated by the observations of von Euler and Liljestrand, who, in 1946, demonstrated a rise in the pulmonary arterial pressure of cats breathing low concentrations of oxygen.[23] In man, we were able to confirm this phenomenon in collaboration first with Motley, Werkö, and Himmelstein.[24] More recently, we established with Fishman, McClement, and Himmelstein[3] that the rise of pressure in the pulmonary artery is associated with some increase in the pulmonary blood flow, but that this increase in flow is not by itself sufficient to account for the change in pressure.

Others have shown that the pulmonary wedge pressure in man, and the left atrial pressure in animals and in man are not altered by hypoxia. There is, therefore, very strong evidence that hypoxia causes pulmonary vasoconstriction.

At what site has this vasoconstriction happened? We are not sure. How is it caused? We do not know. We assume that it arises directly, or indirectly, from the action of a low partial pressure of oxygen at some point in the body.

Is it a local reflex activated at the level of the alveoli or of the pulmonary veins? Does it involve the autonomic system as a result of the stimulation of chemoreceptors in the carotid body or the aorta? Is it due to a direct action of excessively hypoxic mixed venous blood on the precapillary segment of the pulmonary vascular bed? Is there some other vasoconstricting substance liberated in the body under the influence of hypoxemia and carried by venous blood up to the lungs, or is such a substance activated in the pulmonary tissue itself, under the influence of local hypoxia? Does severe hypoxemia cause a shift of blood from the systemic to the pulmonary circulation as a result of systemic vasoconstriction?

Although we are in no way near to a final solution to this problem, there are observations which give a partial answer to some of these questions as far as man is concerned. In the first place, we have not been able to demonstrate a significant increase in central blood volume under the influence of severe arterial hypoxemia. In the second place, we have studied the effect of hypoxia in a patient before and after he underwent extensive bilateral sympathectomy for Raynaud's disease. The sympathectomy, which included the stellate ganglion, the upper three thoracic ganglia on each side, and the mid-cervical ganglion on one side, had no influence on the rise in pulmonary arterial pressure caused by hypoxia. Thus, we tentatively concluded that this effect is not mediated by the sympathetic system.

Liljestrand[25] and von Euler[26] pointed out that, if the pulmonary vascular resistance were regulated on a regional basis by a purely local action of the alveolar and blood oxygen partial pressures, this action could provide an important mechanism for maintaining the most effective ratio of ventilation to perfusion throughout the lungs. To examine this attractive hypothesis, several workers studied the local effects upon blood flow of a hypoxic gas mixture given to one lung in animals; and we, in association with Himmelstein, Fishman, and Fritts,[27,28] made similar observations in man. The technique is difficult because it includes the simultaneous use of bronchospirometry, cardiac catheterization, and arterial cannulation. By means of this technique the flow of blood through each lung separately can be measured.

It was found that concentrations of 8 to 10 per cent oxygen in the inspired gas given to *one* lung caused no modification in the partition of flow of blood between the two lungs, and no change in the pulmonary arterial pressure. Yet, giving a somewhat higher concentration of oxygen (12 per cent) to both sides caused a considerable rise in pressure in the pulmonary artery. Therefore, it seems that any local reflex arising from the low oxygen tension in the alveolar gases has been questioned. The pulmonary capillaries and venules, however, cannot be excluded as a site of origin for such a vasoconstricting reflex, for the calculated oxygen saturation of the pulmonary venous blood on the hypoxic side did not fall below the 80 per cent level, which in bilateral experiments is the critical level for pulmonary hypertension.

We have, however, four observations on the effect of giving concentrations of oxygen as low as 6 per cent to one lung. Here the calculated pulmonary venous oxygen saturation fell below 80 per cent. In three of these studies there was no change in the partition of flow, as compared to the control period. In one of

them there was a diminution of flow to the hypoxic lung; suggestively enough, this is the only instance where mixed venous blood and pulmonary venous blood had an identical oxygen saturation, and where, therefore, no oxygen uptake in the hypoxic lung could be measured. Further work, with even lower oxygen concentration, may resolve the discrepancy between these results and those of experiments on animals in which the giving of pure nitrogen to one lung indisputably caused a diminution in blood flow on this side.

Here, then, the problem of the effects of hypoxia upon the pulmonary vessels lies unsolved, and tantalizing.

b. *Acetylcholine:* I turn now to the effects of acetylcholine on the pulmonary circulation. This drug has been known, since the early experiments of Sir Henry Dale, to have a strong vasodilating influence throughout the systemic arterial tree. As far as the pulmonary circulation is concerned, however, reports on the effects of this preparation in animals have been contradictory. In normal man we found, in collaboration with Harris, Fritts, Clauss, and Odell,[29] that infusion of acetylcholine into the main pulmonary artery at a rate of 0.5 mg. per minute causes a slight, questionable fall in pulmonary arterial pressure. When the pulmonary arterial pressure had been increased previously by hypoxia, however, the fall in pressure due to acetylcholine was very significant, although the hypoxic stimulus was maintained (Fig. 3). This fall in pressure in the pulmonary artery was associated with no change in pulmonary wedge pressure. The cardiac output, which had increased as the result of hypoxia, remained unchanged or rose slightly further. When given in these small amounts, acetylcholine had no effect on the systemic blood pressure or pulse rate, presumably because of its rapid rate of destruction in the blood stream.

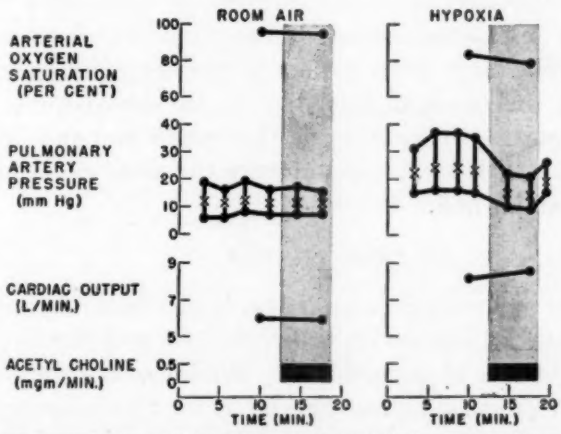

Fig. 3.—Schematic representation of the effects of acetylcholine upon the pulmonary arterial pressure in a normal man. To the left, the subject is breathing 21 per cent O_2 in nitrogen. To the right, he is breathing 12 per cent O_2 in nitrogen. Acetylcholine was given in a continuous infusion of the main pulmonary artery at the rate of 0.5 mg. per minute (shaded area).

It seems fairly certain, therefore, that the action of the drug is limited to the pulmonary circulation, that this action is one of vasodilatation, and that the degree of vasodilatation is largely dependent, as one might expect, on the preexisting tone of the smooth muscles of the pulmonic vessels' wall. As in hypoxia,

we do not know whether the site of action is in the precapillary or the capillary, or in the postcapillary, segments of the pulmonary vascular bed. Again, as in hypoxia, we do not know through what mechanisms the drug acts.

Although they left these questions unsolved, the experiments nonetheless have to their credit important results. They revealed, first, that blood-borne substances can act directly on the wall of some segment of the pulmonary vascular bed; second, that the effects of hypoxia, in causing both an increase in blood flow and a vasoconstriction, can be neatly separated; and third, that the vasoconstriction associated with hypoxia, whatever the site of its action, can be reversed.

INTERPLAY OF FACTORS IN DISEASE

Although I am concerned here mainly with the relative importance of mechanical and vasomotor factors in the pulmonary circulation of normal man, it may be of interest to dwell for a few moments on the question of how such factors are altered by disease. In certain diseases high pressure develops in the pulmonary artery, and this is associated with a high vascular resistance and thickening of the walls of the small branches of the pulmonary artery. The hemodynamics of such a natural experiment provide an interesting contrast to those which hold good under normal conditions. The pulmonary artery pressure of these patients is found to be considerably more dependent on variation in flow and volume than it normally would be, and one may well ascribe this to a diminished distensibility of the thickened pulmonary arterial branches.

The results of experiments with sympathetic blocking agents in this group of diseases have led other workers to assign to the autonomic nervous system an important role in the control of the pulmonary circulation. I am inclined to believe that there are other alternative explanations for the striking drop of pressure in the pulmonary artery following the use of these agents, rather than to claim that it is the result of blocking the nervous supply to the pulmonary vessels. For instance, translocation of even small amounts of pulmonary blood following systemic vasodilatation could have the same effect in a poorly distensible pulmonary vascular bed.

CONCLUSIONS

To summarize our present knowledge, it can be said that we know a great deal about the relations between pressure and flow, and therefore about resistance, in the pulmonary vessels of normal man. We know also that these relations can be influenced by mechanical factors and by at least two chemical stimuli, hypoxia and acetylcholine. However, the mechanism of action of these stimuli is but poorly understood. And, when we come to fit them into an integrated concept of the control of the pulmonary circulation, we are troubled by three great doubts. The first doubt is how far such unphysiologic concentrations of inspired oxygen and doses of acetylcholine throw any light on what happens under normal circumstances. The second doubt is how to extrapolate into indefinite time the results from very short-term observations. The final doubt is whether these results may be justifiably extended to the solution of physiopathologic problems,

when the property of pulmonary vessels and of the surrounding pulmonary tissue have been greatly altered.

Now, what of the future? Perhaps the only incontestable prophecy that can be made is that advances in methodology and advances in understanding will go hand in hand. Any attempt to define the limitations of our present methods of measuring pressure, flow, and volume in the pulmonary circulation points automatically to the directions in which improvements are at the moment being made. For pressure, our hope is for a reliable, pressure-sensitive head to the cardiac catheter. For flow, we look for a method of instantaneous measurement. For volume, we need some much more distinctive quantity than the central blood volume.

As progress is made, more results will pour in. Let us, then, beware of the danger of seeking security for our concepts in the accumulation of facts. As the poet has said:

"Knowledge is proud that it has learned so much,
Wisdom is humble that it knows no more."

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Original Communications

PULMONIC VALVULAR INSUFFICIENCY: A CLINICAL AND HEMODYNAMIC STUDY

PIER F. ANGELINO, M.D., VALERIA LEVI, M.D., AND ANTONIO M. BRUSCA, M.D.

TURIN, ITALY

SINCE the advent of cardiac surgery, accurate diagnosis of cardiac valvular lesions has become not only of academic interest, but also of great practical importance. Therefore, in the past few years a great deal of work has been done in this field. Published observations, however, concerning the clinical and hemodynamic features of pulmonic valve insufficiency are still rather scanty.[1-6]

This report will describe the clinical and hemodynamic features of 7 patients with pulmonary valve insufficiency. These patients have been selected from approximately 2,000 cases of rheumatic and congenital heart disease which have been observed in the cardiac departments of our institutions between 1952 and 1955.

MATERIAL AND METHODS

Three patients had rheumatic heart disease with tight mitral stenosis proved at operation, and 4 had an isolated atrial septal defect.

Each subject was carefully examined and a 12-lead electrocardiogram was routinely performed. X-ray examination included anteroposterior and oblique projections. Angiocardiography was carried out in 6 patients. Cardiac catheterization was done in each subject according to the method of Cournand and Ranges.[7]

The Fick method was employed for determination of cardiac index; formulas for calculation of peripheral resistances and shunts have been reported in previous publications.[8,9]

Patients With Rheumatic Heart Disease and Tight Mitral Stenosis (*Table I*).—This group includes 3 patients, 2 men aged 26 and 37 years, and a 36-year-old woman. A history of repeated bouts of congestive heart failure was present in each patient; one showed signs of cardiac decompensation at the time of the present study. Dyspnea was the main complaint and cyanosis was observed in each instance. Blood pressure was within normal limits, with a tendency to a low pulse pressure. Sinus rhythm was present in every case; one of the patients developed auricular fibrillation during cardiac catheterization following the intravenous administration of reserpine. Stethoacoustic findings included, in each patient, a diastolic rumbling murmur over the apex, with a loud first heart sound and an opening snap of the mitral valve. The second pulmonic

From the Istituto di Patologia Speciale Medica e Metodologia Clinica, Università di Torino, Italy, and from Centro di Cardio-Chirurgia "A. Blalock," Clinica Chirurgica, Università di Torino, Italy.

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sound was greatly accentuated and followed by a high-pitched, blowing, Grade 3 to 4 protodiastolic decrescendo murmur (Fig. 1, *A*). A harsh systolic murmur over the pulmonic area was also present.

On x-ray examination the heart was greatly enlarged in each patient. Cardiac enlargement was due to dilation of the right atrium, right ventricle, and main pulmonary artery; the size of the left ventricle was normal (Fig. 2, *A*). On fluoroscopic examination, no hilar dance could be observed.

The electrocardiogram showed very tall and notched P waves, displaying the features of both "mitral" and "pulmonic" atrial waves (Fig. 3). Right axis deviation of the QRS complex was of extreme degree, ranging between +130 and +140 degrees. The precordial ECG was characterized by a positive QRS complex with tall R waves in right precordial leads and by rS or R/S complexes (Fig. 4) in V_5 and V_6; negative T waves were present as far as in V_4 and V_6. In one case (Case 1) the voltage of the R wave in V_1 was more than 50 mm. (1 mm. V = 1 cm.).

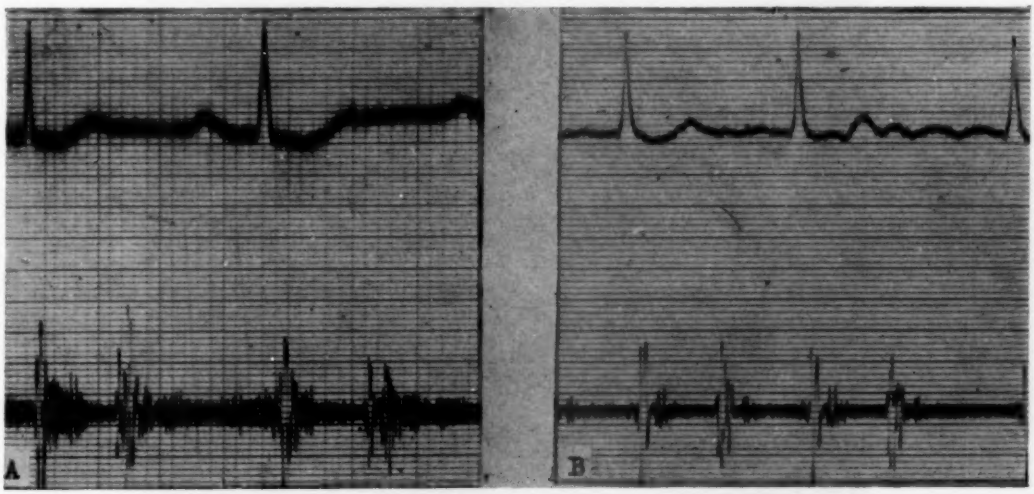

Fig. 1.—Phonocardiogram of Patient 3 (recorded over the pulmonic area, logarithmic microphone. Paper speed 50 mm. per second). *A*, A high-pitched protodiastolic murmur is clearly evident. *B*, Two years after commissurotomy no diastolic murmur is present on the pulmonic area.

Catheterization findings are summarized in Table II. Systolic pressures in the right ventricle were 110-140-135 mm. Hg, and similar systolic values were found in the main pulmonary artery. Hence, no pressure gradient was present between the right ventricle and the main pulmonary artery.

The end diastolic pressures in the right ventricle were 20-28-20 mm. Hg, while in the pulmonic artery diastolic levels of 40-40-55 mm. Hg were recorded, with pulse pressures of 70-100-80 mm. Hg.

In Case 3, the pulmonary circulation was studied before and after the intravenous injection of reserpine. This study was carried out as a part of an investigation the results of which have already been published.[10] Seventy minutes after the injection of the drug into the right ventricle, the systolic pressure in the pulmonary artery dropped from 135 to 65 mm. Hg and the diastolic pressure from 55 to 35 mm. Hg; in the right ventricle, the systolic pressure also dropped from 135 to 65 mm. Hg, and the previously elevated diastolic pressure returned to a normal level (Fig. 5, *A* and *B*). The heart action changed from sinus rhythm to auricular fibrillation, and auscultation no longer revealed the presence of the blowing protodiastolic high-pitched murmur which was audible over the left parasternal area prior to the administration of the drug.

The morphology of the pulmonary artery pressure curves presents certain features which are also seen in pressure pulses recorded in aortic insufficiency (Fig. 6).[11]

In Fig. 6 it can be observed that after an initial notch the pressure reaches its maximum very quickly, giving the ascending limb a steep aspect. The diastolic pressure falls to a low level, quite close to that recorded in the right ventricle.

Angiocardiography showed in each instance greatly enlarged right heart chambers and an enormous dilation of the pulmonary valvular ring, with signs of severe pulmonary arteropathy (Fig. 7).

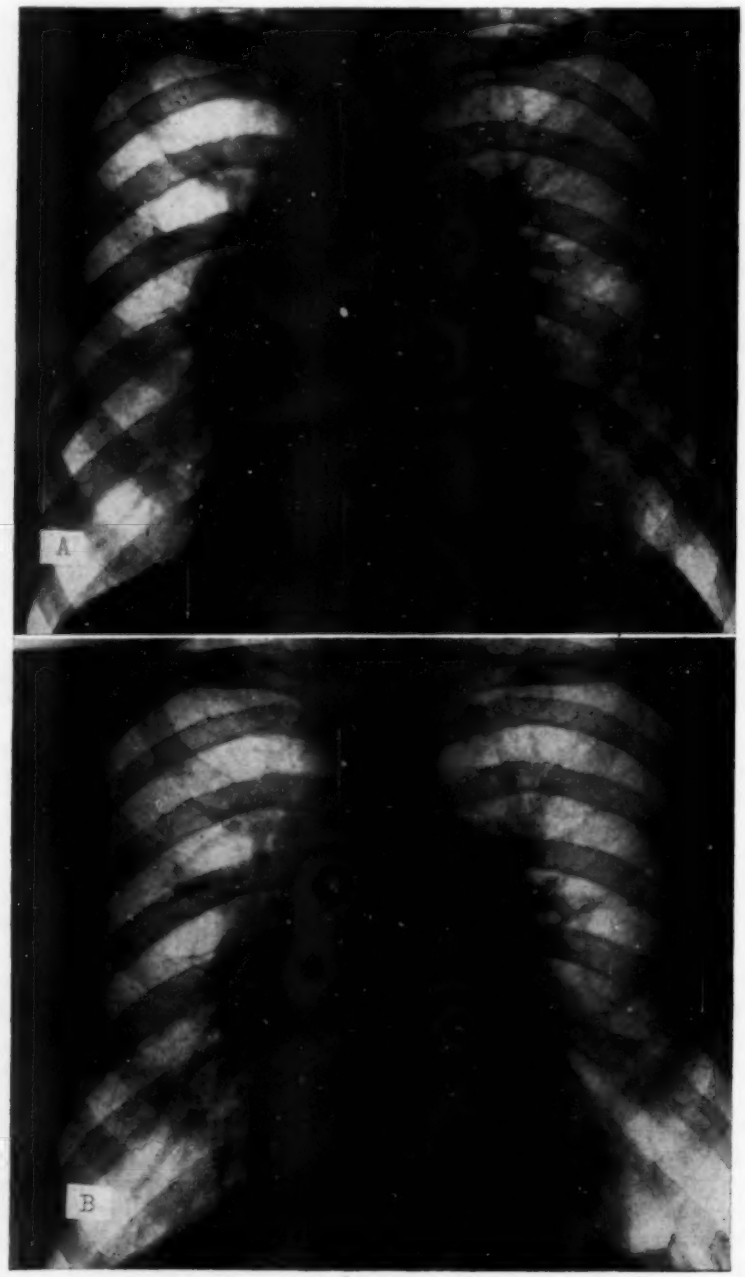

Fig. 2.—*A*, Preoperative x-ray picture (anteroposterior projection) in Patient 1. Note the markedly enlarged pulmonary artery. *B*, The same patient one year after commissurotomy.

Mitral commissurotomy was performed in these 3 cases, and extremely tight stenosis was found in each. Twenty to thirty days after mitral valvulotomy, the pulmonic diastolic murmur had completely disappeared in each case, but the systolic murmur was still present. Two years after surgery no murmurs could be detected in the pulmonic area (Fig. 1, *B*).

Patients With "Isolated" Atrial Septal Defect (*Table III*).—This group includes 4 patients. In every case the diagnosis was proved by the passage of the intracardiac catheter from the right to the left atrium. No other cardiac abnormalities could be demonstrated. Three patients were female, one a male. The youngest patient was 9 years old and the oldest was 29. Dyspnea after exertion was present in every case; 2 patients had had hemoptysis; a history of right heart failure was elicited in 2 cases.

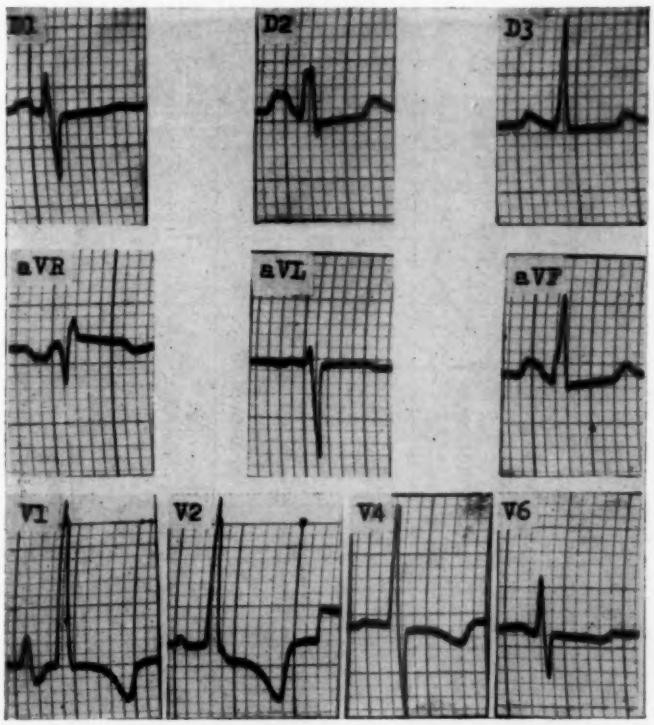

Fig. 3.—Electrocardiogram of Patient 1.

One patient had rather severe cyanosis of the lips, ears, fingernails, and mucous membranes. Three patients were in regular sinus rhythm and one had auricular fibrillation.

Blood pressure determinations were within normal limits. The heart was markedly enlarged in each instance. Auscultation revealed a harsh systolic murmur over the apex in 3 cases; a systolic murmur was recorded over the pulmonic area in each case; in 2 patients this systolic murmur was "diamond" shaped. An accentuated second pulmonic sound was recorded in 2 instances. In every case a diastolic murmur was present over the left parasternal area; this murmur was quite loud (Grade 4) in 3 patients, highly pitched, starting in the early diastolic phase (Fig. 8, *A*). Hepatomegaly was observed twice.

On x-ray examination the prominent findings were (1) marked dilation of the right atrium, right ventricle, and pulmonary artery, and (2) obvious dance of the hilar vessels.

Angiocardiography performed in 3 cases confirmed the extreme enlargement of the right heart chambers and pulmonary vessels. In 2 cases the right and the left atria were simultaneously visualized.

The electrocardiogram showed very tall and peaked P waves in Leads S_2, S_3, aVF, and V_1.

TABLE I

NAME AGE SEX	DIAGNOSIS	DYSPNEA	HEPATO-MEGALY	HEMOP-TYSIS	STETHOSCOPIC FINDINGS		X-RAY FINDINGS					ELECTROCARDIOGRAM		
					APEX	PULMONARY AREA	R.A.	R.V.	P.A.	L.A.	L.V.	RHYTHM	QRS-AXIS DEVIATION	R.V.H.
1. F.A. 26 years Male	R.H.D. E.H. M.S.-P.I. R.S.R. IV°	+++	+	−	Diastolic rumble	Systolic-diastolic murmur	+	++	+++ +	+++	−	R.S.R.	+140°	+++
2. C.L. 37 years Male	R.H.D. E.H. M.S.-P.I. R.S.R. IV°	+++	++	++	Diastolic rumble	Systolic-diastolic murmur	++	++	+++ +	+++	−	R.S.R.	+130°	+++
3. B.G. 36 years Female	R.H.D. E.H. M.S.-P.I. R.S.R. IV°	+++	++	++	Diastolic rumble	Systolic-diastolic murmur	+	++	+++ +	++	−	R.S.R.	+130°	+++

M.S. = mitral stenosis; R.H.D. = rheumatic heart disease; R.A. = right atrium; R.V. = right ventricle; P.A. = pulmonary artery; L.A. = left atrium; L.V. = left ventricle; R.V.H. = right ventricular hypertrophy; P.I. = pulmonary insufficiency; E.H. = enlarged heart; R.S.R. = regular sinus rhythm.

TABLE II

NAME AGE SEX	DIAGNOSIS	O_2/MIN./M.^{2}	CARDIAC INDEX	R.A.P.		R.V.P.			P.A.P.			P.C.P.			T.P.R. DYNES-SECONDS/CM.$^{-5}$
				S	D	S	D	M	S	D	M	S	D	M	
1. F.A. 26 years Male	R.H.D.–E.H. M.S.–P.I. R.S.R. IV°	150	2.40	10	4	110	5–20	52	110	40	70	35	18	25	1,503
2. C.L. 37 years Male	R.H.D.–E.H. M.S.–P.I. R.S.R. IV°	160	1.32	15	5	140	5–28	62	140	40	60	38	30	25	2,742
3. B.G. 36 years Female	R.H.D.–E.H. M.S.–P.I. R.S.R. IV°	130	2.07	22	4	135	20	60	135	55	85	42	28	35	2,062

R.A.P. = right atrium pressure; R.V.P. = right ventricular pressure; P.A.P. = pulmonary artery pressure; P.C.P. = pulmonary capillary pressure; T.P.R. = total pulmonary resistances.

TABLE III

NAME AGE SEX	DIAGNOSIS	DYSPNEA	HEMOPTYSIS	HEPATOMEGALY	STETHOSCOPIC FINDINGS		X-RAY FINDINGS					E LECTROCARDIOGRAM		
					APEX	PULMONIC AREA	R.A.	R.V.	P.A.	L.A.	L.V.	RHYTHM	QRS-AXIS DEVIATION	R.V.H.
4. B.A. 15 years Female	C.H.D. E.H. A.S.D. P.I. R.S.R. II°	+	+	−	Systolic murmur	Systolic-diastolic murmur	++	++	++ ++	−	−	R.S.R.	−	Focal block
5. T.A. 29 years Female	C.H.D. E.H. A.S.D. P.I. A.F. III°	++	+	++	Systolic-diastolic murmur	Systolic-diastolic murmur	++	++	++	−	−	A.F.	+100	+
6. P.R. 9 years Male	C.H.D. E.H. A.S.D. P.I. R.S.R. II°	±	−	−	−	Systolic-diastolic murmur	++	++	++ +	−	−	R.S.R.	+ 90	Focal block
7. A.F. 21 years Female	C.H.D. E.H. A.S.D. P.I. R.S.R. IV°	++	−	++	Systolic murmur	Systolic-diastolic murmur	++ +	++	++ +	−	−	R.S.R.	+120	+

R.A. = right atrium; R.V. = right ventricle; P.A. = pulmonary artery; L.A. = left atrium; L.V. = left ventricle; R.V.H. = right ventricular hypertrophy; C.H.D. = congenital heart disease; A.S.D. = atrial septal defect; P.I. = pulmonary insufficiency; E.H. = enlarged heart; R.S.R. = regular sinus rhythm; A.F. = auricular fibrillation.

TABLE IV

NAME AGE SEX	DIAGNOSIS	O_2/MIN./M.^{2}	PERIPHERAL BLOOD FLOW (L./MIN.)	SYSTEMIC CARDIAC INDEX (L./MIN./M.^{2})	P.B.F.	R.A.P.		R.V.P.			P.A.P.			P.C.P.			T.P.R. DYNES-SECONDS/CM.$^{-5}$	SHUNT	
						S	D	S	D	M	S	D	M	S	D	M		R-L	L-R
4. B.A. 15 years Female	C.H.D.-E.H. A.S.D.-P.I. R.S.R. II°	156	3.90	2.79	4.910	8	2	40	0–10	20	25	0	18	10	5	8	228	0.52	1.53
5. T.A. 20 years Female	C.H.D.-E.H. A.S.D.-P.I. A.F. III°	135	3.56	2.30	6.516	20	8	75	0–20	45	48	0	30	15	6	10	740	0.40	3.70
6. P.R. 9 years Male	C.H.D.-E.H. A.S.D.-P.I. R.S.R. II°	158	4.23	2.34	9.200	5	0	38	0–7	20	25	4	14	12	7	9	121	0.75	6.62
7. A.F. 21 years Female	C.H.D.-E.H. A.S.D.-P.I. R.S.R. IV°	160	3.15	2.10	—	32	28	135	0–32	70	135	55	100	45	30	40		—	—

R.A.P. = right atrium pressure; R.V.P. = right ventricular pressure; P.A.P. = pulmonary artery pressure; P.C.P. = pulmonary capillary pressure; T.P.R. = total pulmonary resistances; R-L = right-to-left shunt in liters per minute; L-R = left-to-right shunt in liters per minute; P.B.F. = pulmonary blood flow in liters per minute.

Axis deviation of the QRS complex ranged between +90 and +120 degrees; the precordial ECG was characterized by a "focal block" pattern in 2 cases and by the presence of marked right ventricular hypertrophy in the other 2.

In Cases 4, 5, and 6, the hemodynamic picture (Table IV) was characterized by the presence of a left-to-right shunt, with overloading of the pulmonary circulation, without obvious signs of pulmonic vessel involvement; none of these patients was cyanotic. In Case 7, on the contrary, a predominant right-to-left shunt was demonstrated.

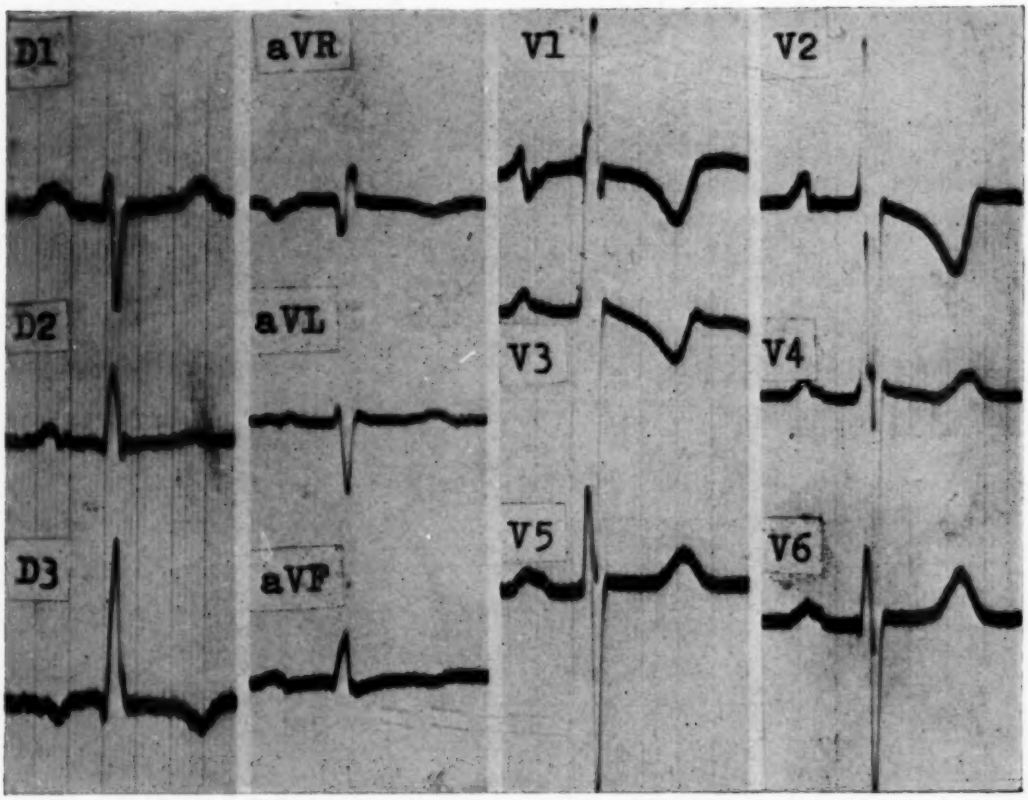

Fig. 4.—Electrocardiogram of Patient 2.

In Cases 4, 5, and 6, systolic pressures of 25-48-25 mm. Hg were recorded in the pulmonary artery, and systolic pressures of 40-75-38 mm. Hg in the right ventricle. This indicates a systolic pressure gradient of 15-27-13 mm. Hg across the pulmonic valve (Fig. 9). In Case 7 systolic pressures were equal in the pulmonary artery and the right ventricle.

In the pulmonary artery, diastolic pressures were 0-0-4 mm. Hg in Cases 4, 5, and 6, and 55 in Case 7; in this last case systolic pressure was also markedly elevated (135 mm. Hg). In the right ventricle diastolic pressures of 0 were recorded in each instance during the early diastolic phase, with a subsequent rise to 10-20-7-32 mm. Hg.

In Case 4 a surgical closure of the septal defect was performed under direct vision. Following surgery a good clinical improvement was observed, but the auscultatory findings did not change and a systolodiastolic murmur over the pulmonic area was still present 1 year after the operation (Fig. 8, *B*).

DISCUSSION

In the 7 patients (3 with mitral stenosis and 4 with atrial septal defect) reported upon in the present study, the diagnosis of valvular pulmonic insufficiency

was made on the basis of (1) presence of high-pitched protodiastolic murmur over the pulmonic area, (2) clinical, radiographic, and electrocardiographic signs of marked right ventricular hypertrophy with pulmonary congestion, (3) absence of any evidence of aortic valvular disease, and (4) elevated pulmonary pulse pressure and, in 4 cases, pulmonary diastolic levels very close or equal to right intraventricular diastolic pressure.

From a clinical standpoint, patients with mitral stenosis complicated by pulmonic valve insufficiency showed marked impairment of their cardiocirculatory functions. This is in keeping with Friedberg's [12] observations on the serious

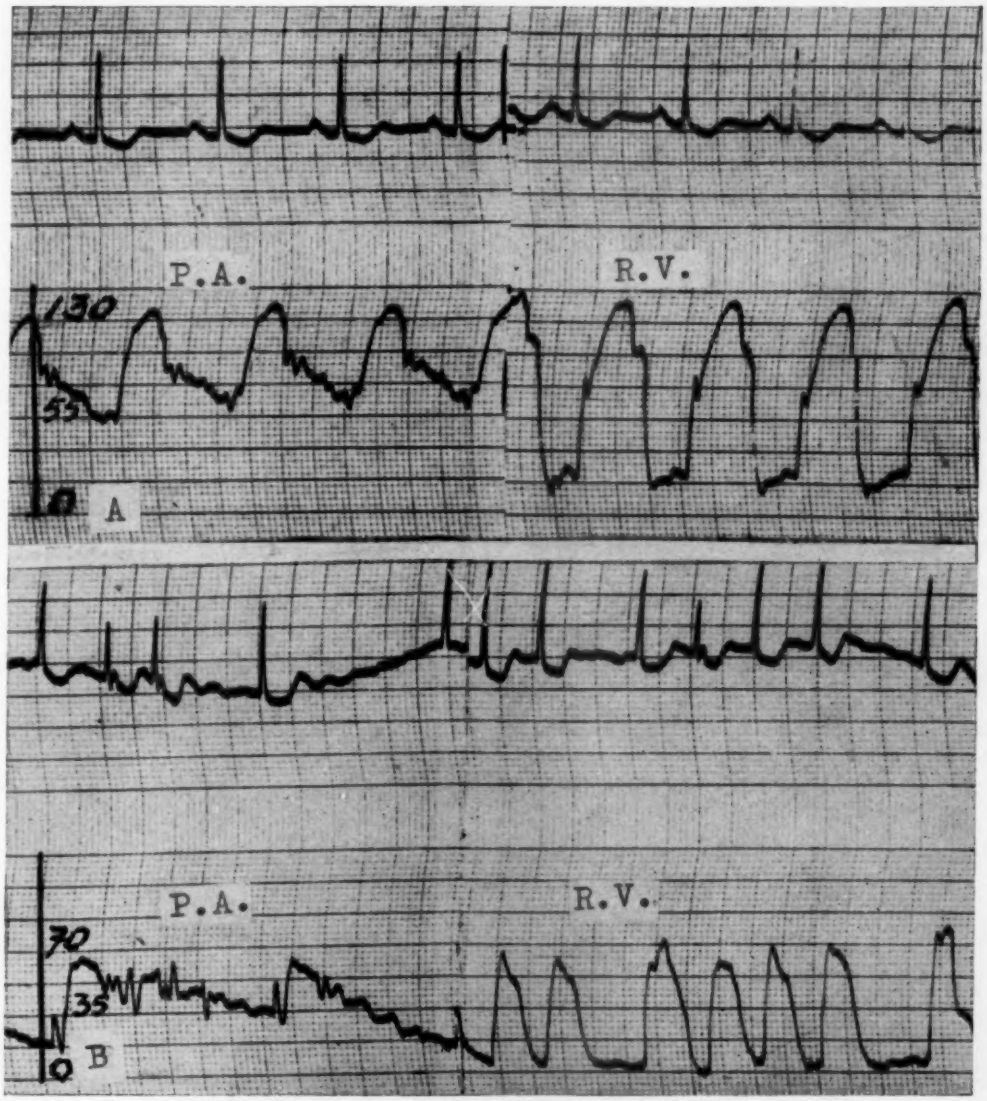

Fig. 5.—Hemodynamic changes induced in the pulmonary artery (*P.A.*) and right ventricle (*R.V.*) by the acute administration of reserpine (2 mg. intravenously). *A*, Prior to administration of the drug. *B*, Seventy minutes after the injection (explanation in the text).

prognosis involved with this type of lesion and may well be explained on the basis of the severe degree of pulmonary hypertension which, as a rule, accompanies pulmonary valve insufficiency complicating mitral stenosis. On the other hand, it is understandable how regurgitation through the incompetent pulmonary valves may impose a further strain on the overloaded right ventricle. Furthermore, in each of our patients with mitral stenosis and pulmonary insufficiency the mitral orifice was found by the surgeon to be extremely narrow.

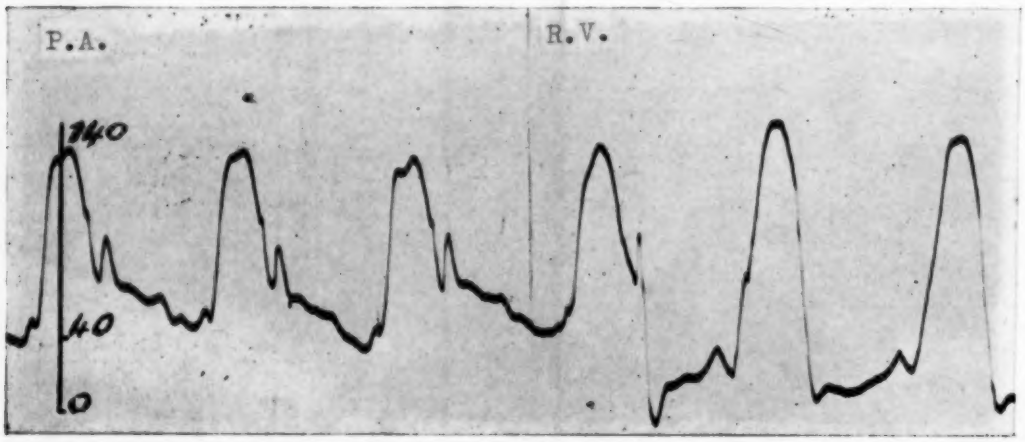

Fig. 6.—Pressure pulses in the pulmonary artery (*P.A.*) and in the right ventricle (*R.V.*) in a case of mitral stenosis with pulmonic valve insufficiency (Case 2).

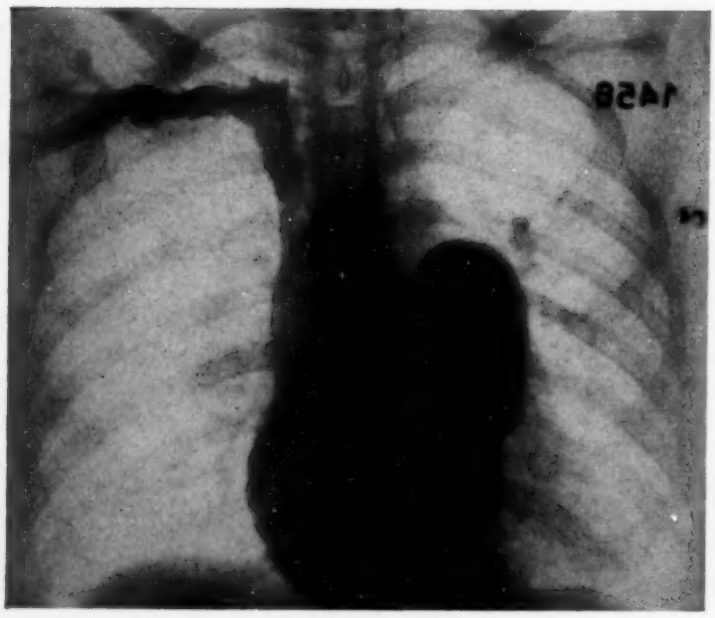

Fig. 7.—Angiocardiography in Patient 1 (radiogram taken 2 seconds after the injection of the contrast material in the cubital vein). The main pulmonary artery is enormously enlarged and the pulmonary ring is greatly dilated. The shadows of the semilunar valves are clearly outlined.

In these patients a markedly elevated systolic pressure was recorded in the pulmonary artery. Pulse pressure was also increased; this was due not only to the elevated systolic pressure, but also to a diminution of the diastolic level. From an analysis of some of the published data obtained from large series of patients[8,13] it has been observed that diastolic pressure, in cases with pulmonary hypertension, usually is not less than 50 per cent of the systolic value. In the cases described in this paper, diastolic pressures in the pulmonary artery were 36, 28, and 40 per cent of the systolic pressure. However, pulmonary diastolic readings were still well above diastolic values in the right ventricle. This phe-

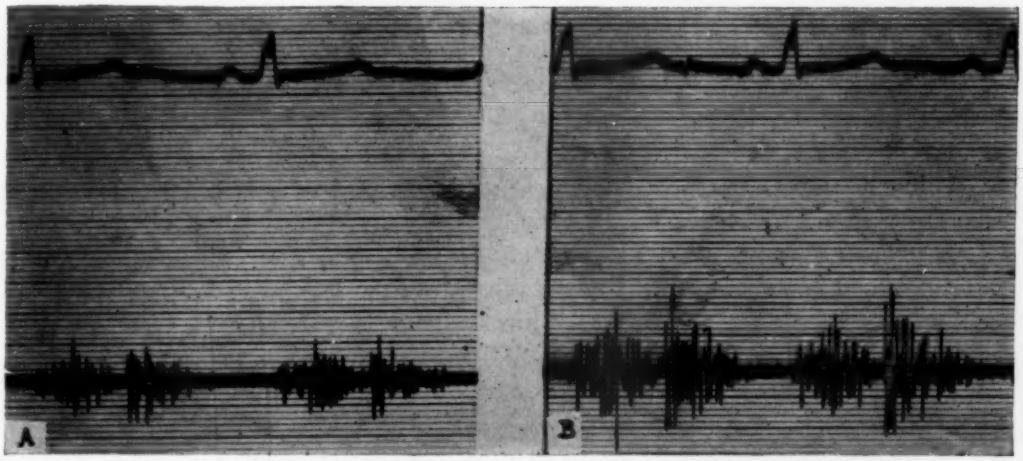

Fig. 8.—Phonocardiogram recorded over the pulmonic area in a case of isolated atrial septal defect with pulmonic valve insufficiency (Case 4) (logarithmic microphone, paper speed 50 mm. per second). *A*, Note the "diamond-shaped" systolic murmur and the high-pitched protodiastolic murmur. *B*, Phonocardiogram recorded in the same patient 2 months following the surgical closure of the atrial defect; the auscultatory findings have not changed significantly.

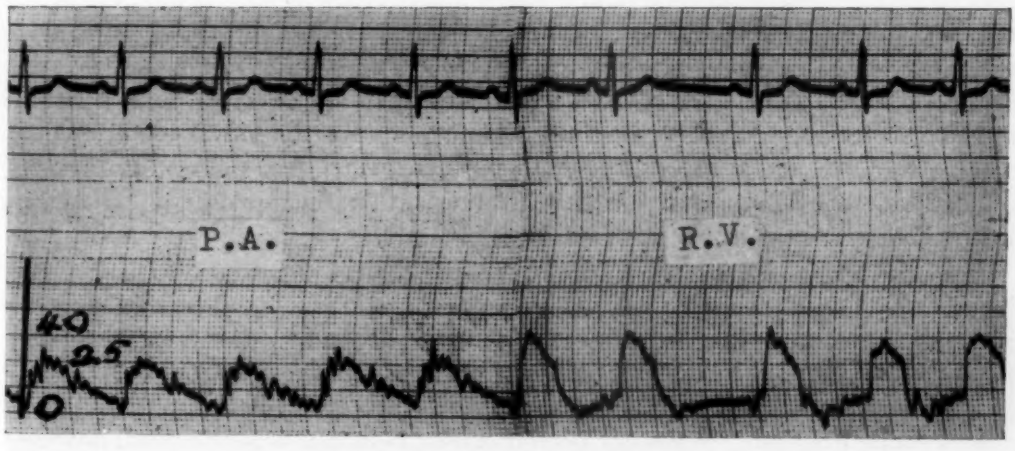

Fig. 9.—Pressure pulses in the pulmonary artery (*P.A.*) and in right ventricle (*R.V.*) in a patient with atrial septal defect and pulmonary valve insufficiency (Case 4). Note diastolic readings in the pulmonary artery equal to the diastolic levels in the right ventricle. There is a pressure gradient of 15 mm. Hg between systolic pressure in the right ventricle and systolic pressure in the pulmonary artery.

nomenon can be explained on the basis of the elevated pulmonary resistances. On the other hand, particularly in the presence of high systolic values, pulmonary valve insufficiency, as well as aortic valve insufficiency, does not necessarily imply that the diastolic pressure in the vascular circuit should equal the diastolic pressure in the ventricular chamber.

The morphologic aspect of the curves recorded in the pulmonary artery was similar to that reported by other authors.[5,6] Because of the limitations of our present methods of recording, however, one cannot rely too much on this type of analysis.

In 3 of our 4 cases with atrial septal defect and pulmonary insufficiency, the clinical as well as the hemodynamic situation was quite different from that observed in the other cases with the same valvular lesion complicating mitral stenosis. In the former group cardiocirculatory impairment was not so pronounced, and systolic pressure readings in the pulmonary artery were only slightly elevated or normal.

Diastolic levels in the pulmonary artery were practically equal to levels recorded in the right ventricle. This cannot be caused only by lowered pulmonary resistances, as suggested by Kjellberg and co-workers.[14] In fact, in an analysis of 40 cases of isolated interatrial septal defect we have never found diastolic pressures in the pulmonary artery as low as diastolic pressures in the right ventricle.[15]

Pulmonary hypertension was present only in one of the cases with atrial septal defect; this patient (No. 7) was cyanotic, and a predominant right-to-left shunt was demonstrated.

There is no doubt that in the patients with mitral stenosis the pulmonary valve incompetence is strictly related to the pulmonary hypertension with dilation of the pulmonary valvular ring (Fig. 7). This view is supported by the disappearance of the murmur of pulmonic insufficiency following operation in each of our cases (Fig. 1, *A* and *B*). Furthermore, the role of pulmonary hypertension in the genesis of pulmonary valve insufficiency is well demonstrated by the effect of the acute administration of reserpine in one of our cases. Following the intravenous injection of 2 mg. of the drug, the systolic pulmonary pressure dropped from 135 to 65 mm. Hg, with a fall of pulse pressure from 80 to 30 mm. Hg (Fig. 5), and the protodiastolic murmur over the left parasternal area disappeared. Systolic arterial pressure and cardiac index did not change significantly; three hours after cardiac catheterization the murmur of pulmonary insufficiency was again heard in its original site.

In the group of patients with atrial septal defect the most consistent findings were (1) pulmonary diastolic pressure practically equal to the diastolic pressure in the right ventricle, and (2) an abnormal gradient between the systolic pressures in the right ventricle and pulmonary artery. Anatomic control is lacking in our cases, so that an organic lesion cannot be ruled out as a cause of this pressure gradient. A similar hemodynamic behavior was observed, however, after experimental destruction of pulmonary valves in dogs[16] and in other published cases of pulmonary valvular insufficiency in which no stenosis could be found on post-mortem examination.[4,6,17]

SUMMARY AND CONCLUSION

Seven cases of pulmonary valve insufficiency have been studied from the clinical and hemodynamic standpoint.

Three of these patients had rheumatic heart disease with pure mitral stenosis and four had an isolated atrial septal defect.

In each of the cases with mitral stenosis and pulmonary insufficiency a high degree of pulmonary hypertension was present and the mitral valvular orifice was found by the surgeon to be extremely narrow. In these patients mitral commissurotomy was followed by remarkable clinical improvement. These findings suggest that the presence of pulmonary insufficiency in patients with mitral stenosis is an indication of marked pulmonary hypertension and that, if no other contraindications are present, mitral commissurotomy is in order.

In patients with atrial septal defect and pulmonary insufficiency, pulmonary pressure may not necessarily be elevated. The most consistent findings in these patients were (1) pulmonary diastolic levels very close to the diastolic levels in the right ventricle, and (2) a gradient between the systolic pressure in the right ventricle and the systolic pressure in the pulmonary artery.

As suggested by other workers, this pressure gradient does not necessarily indicate the presence of an organic pulmonary stenosis.

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CYANOSIS IN MANSON'S SCHISTOSOMIASIS

Role of Pulmonary Schistosomatic Arteriovenous Fistulas

J. Lopes de Faria, M.D.,* Juljian Czapski, M.D.,** M. O. Ribeiro Leite, M.D.,** D. de Oliveira Penna, M.D.,** T. Fujioka, M.D.,** and A. B. de Ulhôa Cintra, M.D.**

São Paulo, Brazil

CYANOSIS has been described in schistosomal chronic "cor pulmonale." However, even in this condition it is not a common manifestation.[1,2,8,9,11,12] Its presence has been attributed to right heart failure,[1,9,11,12] and its relative infrequency may be due to the absence of diffuse and severe sclerosis of the pulmonary capillaries.[6]

In a previous paper, one of us[5] described the formation of pulmonary arteriovenous fistulas through the necrotizing action of embolic schistosome ova on the small pulmonary arteries and adjacent pulmonary veins. The role of these A-V fistulas in the arterial distribution of schistosome ova was the object of a paper in one of the cases to be reported.[7] In our experience there is an increasing number of schistosomiasis patients in whom the finding of marked cyanosis cannot be explained by an existing schistosomatic "cor pulmonale."

The purpose of this paper, which is based on two cases with necropsy, is to emphasize the importance of these fistulas as a major factor in the pathogenesis of cyanosis in certain patients with Manson's schistosomiasis.

CASE REPORTS

Case 1—J. Z. R., a 22-year-old white Brazilian woman from the northeastern state of Alagoas, was admitted on Dec. 6, 1954, to "Hospital das Clínicas." On admission a left lower lobe bacterial pneumonia was recognized and successfully treated with penicillin. The patient stated that a diagnosis of Manson's schistosomiasis had been established 4 years previously at another hospital. A splenectomy had been performed 3½ years prior to this admission. About 1 year after operation the patient started having repeated episodes of cough with small amounts of yellowish sputum, and cyanosis was noticed which persisted up to the time of admission. Lately, some shortness of breath on strenuous exercise was noticed.

On physical examination, aside from the typical syndrome of lower left lobe consolidation (lobar pneumonia), important findings were a marked cyanosis (of the so-called central type) which persisted after the cure of the pneumonia. There were also some "spider angiomas" on the anterior walls of chest and abdomen, slight clubbing of fingers; a firm, enlarged liver, palpable 5 cm. below the right costal margin; an old splenectomy scar. No signs of heart failure were found.

This patient stayed in the ward for 6 months, being studied and given treatment. After

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*From the Department of Pathology, Faculty of Medicine, University of São Paulo.
**From the Hospital das Clínicas, Faculty of Medicine, University of São Paulo.

that time massive esophageal bleeding occurred, which could not be controlled with the use of blood transfusions or balloon tamponade of the terminal esophagus. The patient died after being in hepatic coma for 2 days.

A number of laboratory and auxiliary tests were done, the more important being given here. (1) Oxymetric studies on blood, repeated a number of times, revealed unsaturations of 74 per cent on arterial blood and 64 per cent on venous blood. After receiving oxygen for half an hour (nasopharyngeal catheter), arterial saturation rose to 96 per cent and venous blood was still 64 per cent saturated. (2) ECG's were essentially normal, although some observers felt there was some suggestion of left ventricular strain (Fig. 1). (3) X-ray studies of heart and great vessels showed a nonenlarged cardiac shadow, presenting only some bulging of the pulmonary artery area. Vascular markings in both lung fields were rich, although no pathologic increase was felt to be present (Fig. 2). (4) Cardiac catheterization was performed, and although no exercise determinations could be obtained, for technical reasons, the pressures at rest ("PC," pulmonary artery, right ventricle, right atrium, venae cavae) were all inside the limits of normal. (5) Pulmonary function tests gave normal results both for ventilatory and alveolorespiratory functions. Only a decrease of alveolar CO_2 was found, which was interpreted as indicating diminished venous blood flow to the alveolar area. (6) Angiocardiography ("Cilatrast" 70 per cent, 60 ml.) was performed and a rather peculiar picture was obtained which at the time could not be interpreted diagnostically.

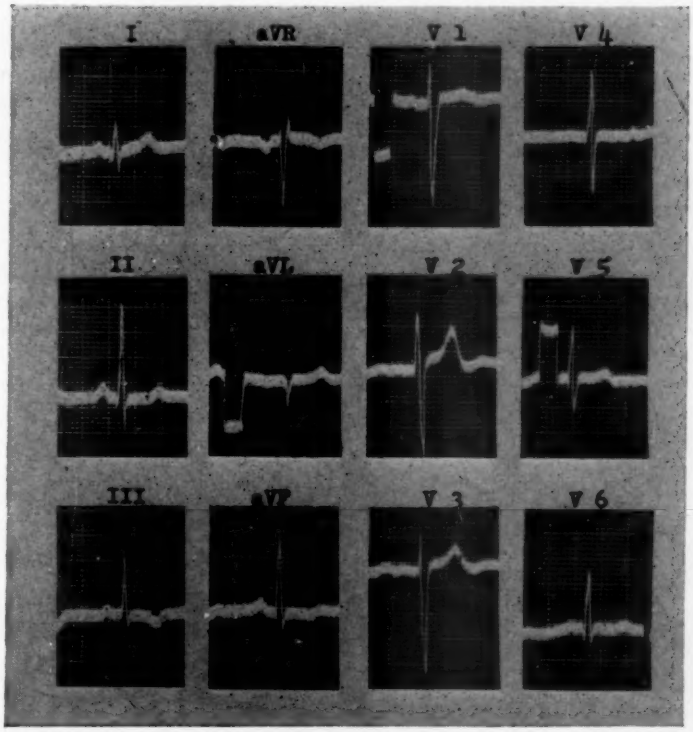

Fig. 1.—Electrocardiogram in Case 1.

The arterial branching of the pulmonary vessels presented a "lacework" aspect, conferring a granular pattern. Besides, contrast was observed to persist in the pulmonary vessels for an increased time, giving the same granular aspect even at the eighth plate, taken 9.6 seconds after injection of the contrast medium (Fig. 3). (7) Serum chloride levels were high (115.9, 110, 114.1, 108.4 meq./ L.) and CO_2 combining power was somewhat lowered (38.5, 44.7, 36.2 vol. per cent in venous blood). Sodium and potassium in the plasma were normal.

Necropsy.—Cadaver weighed 53 Kg. and was 160 cm. in height. An old scar of splenectomy was seen. Cyanosis and clubbing of finger tips were present. The heart, weighing 300 grams,

presented only a slight hypertrophy of the left ventricle, the right being normal. The lungs, each one weighing 600 grams, showed hyperemia, moderate edema, collapse of both lower lobes, and a few bronchopneumonic foci in the left lung; bronchial obstruction was absent. There was no fluid accumulation in the serous cavities. There had been a recent gastrostomy with slight diffuse serofibrinous purulent peritonitis (300 ml. of fluid free in the peritoneal cavity). The lesser curvature of the stomach presented a chronic peptic ulcer. The liver, 1,440 grams in weight, showed the picture of the so-called schistosomal cirrhosis, involving in the fibrotic process, the large and mainly the small portal spaces. The kidneys were enlarged, hyperemic, weighing 160 and 180 grams, respectively.

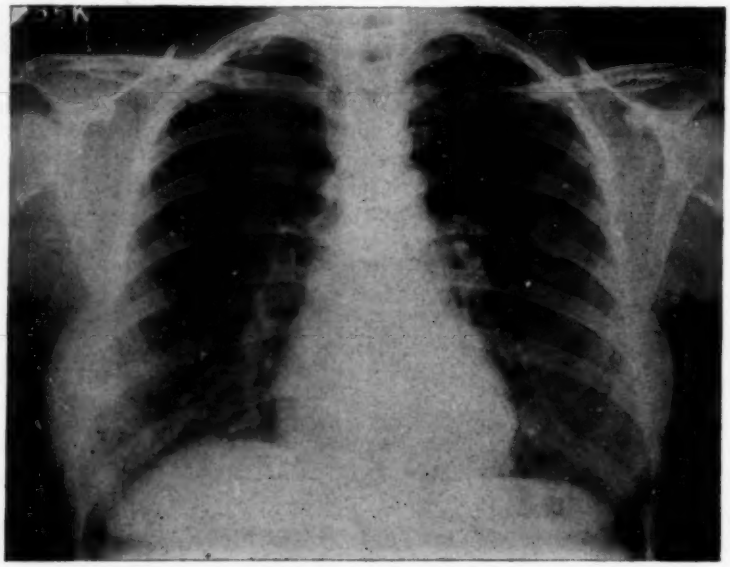

Fig. 2.—Chest roentgenogram in Case 1.

Microscopic Examination.—The lungs (sections taken from 5 different blocks) showed numerous lesions caused by schistosome ova, i.e., granulomas, scars from granulomas, and mainly destructive lesions in the walls of the pulmonary arteries. The granulomas or scars were found around small pulmonary arterial branches, in the peribronchial connective tissue and in the alveolar septa; occasionally, ova were detected in the alveolar lumina. The involved pulmonary vessels were mainly small arteries and arterioles (between 40 and 200 μ in diameter). They presented an old destructive process of the wall through which frequently a communication with adjacent venules was observed (arteriovenous fistulas), as shown in Fig. 4. Not rarely this communication was not found in a single section, but only in serial sections. In a single section was seen only the involved artery surrounded by very dilated venules (compare with Fig. 6). The venules forming these A-V fistulas presented very thin walls made by endothelium, a discontinuous elastic membrane, and a thin collagenous layer. Frequently a part of the latter was in immediate contact with pulmonary alveoli (Fig. 5). Pulmonary capillaries with very wide lumina were commonly seen in communication with such venules. A few small arteries and arterioles showed slight collagenous thickening of the intima, without lumen narrowing, related to ova passage. Occasional precapillaries presented intense intimal fibrous thickening with lumen narrowing and without relation to ova. The picture of active endarteritis, as well as hyaline thrombi, was not found. Pulmonary capillaries were hyperemic and dilated, without any thickening of their basal membrane. A few pulmonary areas showed alveolar edema, others alveolar collapse. Rare bronchopneumonic foci were noticed. The liver showed schistosomal cirrhosis; there was no passive hyperemia. The rectum gave the picture of schistosomal rectitis, with many schistosome ova. The kidney presented acute diffuse glomerulonephritis.

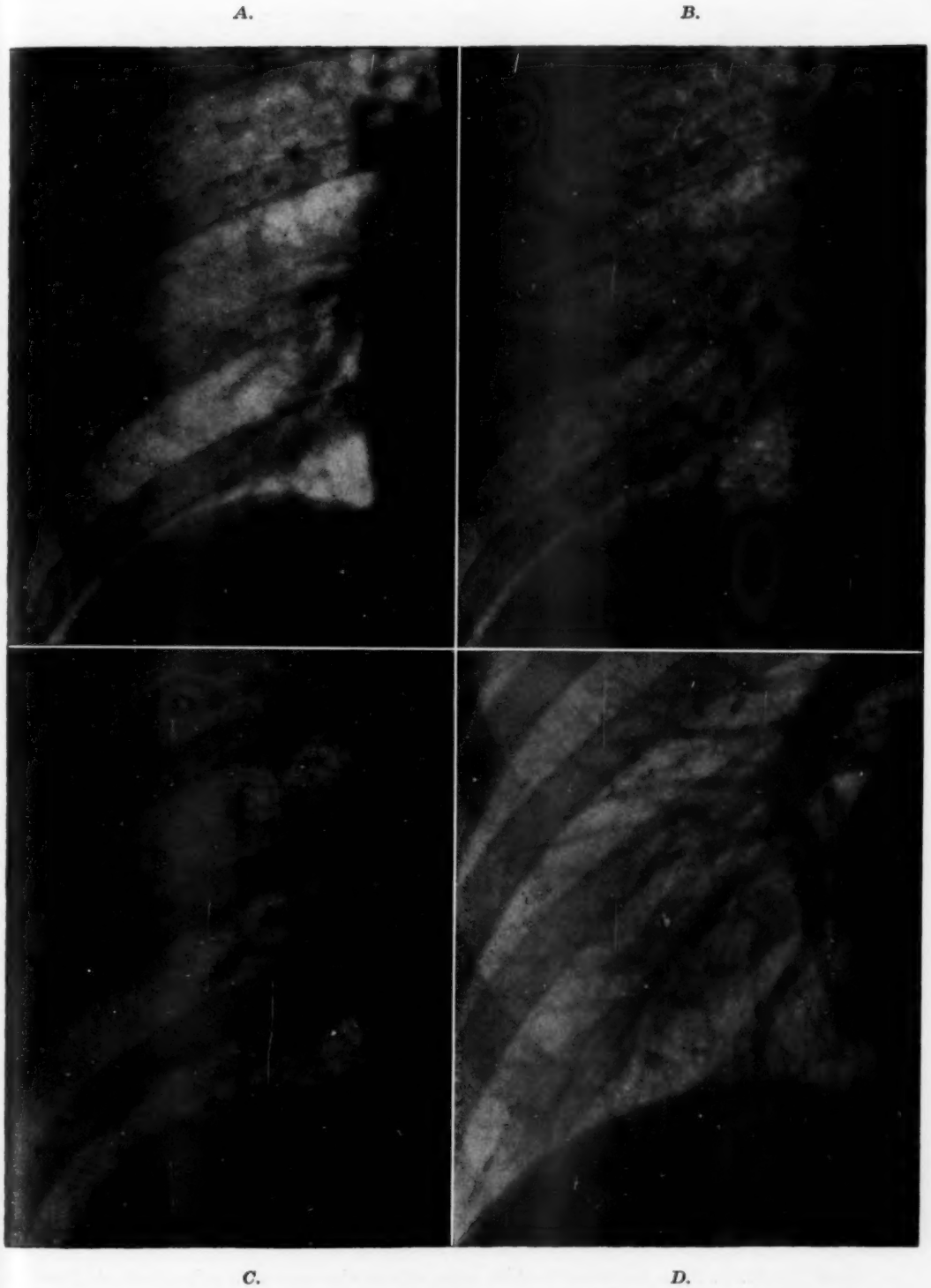

Fig. 3.—Case 1. Angiocardiogram. *A* **is taken 1.2 seconds after injection.** *B*, **taken 3.6 seconds after injection, demonstrates the "lacework" aspect of the pulmonary vessels, conferring a granular pattern to the plate.** *C*, **taken 8.4 seconds after injection, shows delayed persistence of contrast in the pulmonary circuit (a similar aspect could be detected even 9.6 seconds after injection).** *D* **shows the angiocardiographic aspect at 3.4 seconds in a normal patient.**

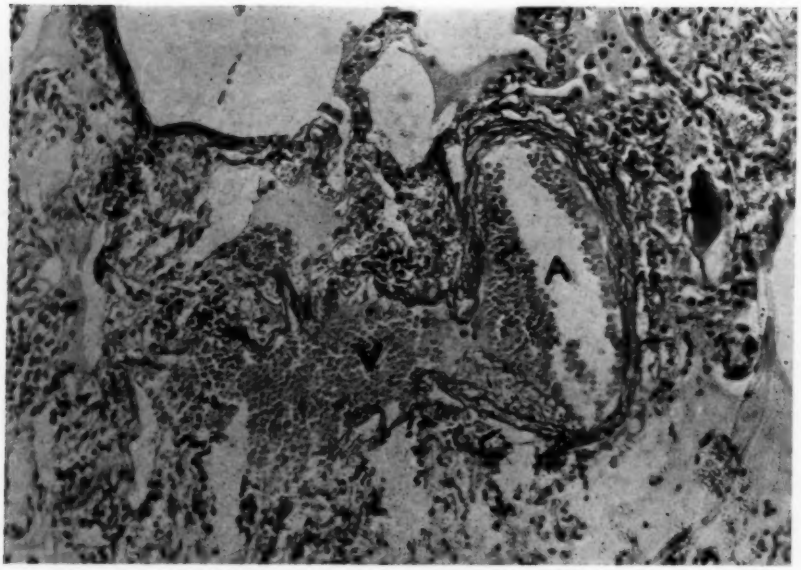

Fig. 4.—Case 1. Schistosomatic pulmonary arteriovenous fistula. A schistosome ovum is seen just to the right of the arterial wall. *A* indicates the arterial lumen; *V*, the venous lumen. The arterial intima shows a conspicuous thickening at the opening into the vein. (Weigert's elastic tissue and van Gieson's stains; ×230.)

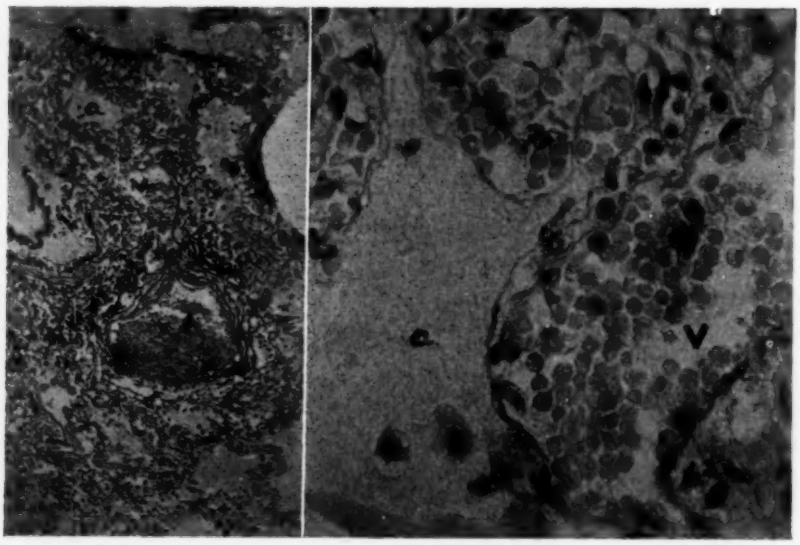

Fig. 5.—Case 1. At left there is a schistosomatic pulmonary arteriovenous fistula. (The communication between the arterial lumen *A*, and the venous one, *V*, does not appear in this section.) *a* = pulmonary alveolus. (Weigert's elastic tissue and van Gieson's stains; ×76.) On the right, a higher magnification of the venule (*V*) is presented, to show its relation to the alveolar lumen (*a*). (×395.)

CASE 2.—M. F. B., a 25-year-old white woman from the state of Sergipe, was admitted on Feb. 10, 1955. About 8 years before, the patient had undergone splenectomy; for 2 years prior to operation the patient had been aware of a mass in the left subcostal region which had increased in size slowly but progressively, and turned out to be a large schistosomatic spleen. For the last 4 years some shortness of breath appeared during exercise, and cyanosis of lips and fingernail beds

was noticed. One month prior to admission the patient had an episode of hematemesis and this was the chief reason for seeking medical care.

Physical examination revealed an undernourished patient, presenting marked cyanosis with clubbing of the fingers. Lungs were clear. The apex impulse was felt in the fourth left intercostal space medially to the mid-clavicular line. A soft systolic murmur was heard in the mitral area. The liver was palpable 3 cm. below the right costal margin.

After 1 month in the ward, the patient had a massive bleeding from ruptured esophageal varices. All therapeutic efforts were of no avail and the patient died.

Diagnostic tests included the following procedures. (1) Oxymetry of blood revealed a saturation of 82 per cent on arterial blood and 76 per cent for the venous blood. After half an hour of receiving oxygen by catheter those figures rose to 97 and 80 per cent, respectively. (2) ECG was normal. (3) Heart and great vessels were normal on x-ray studies. Vascular markings in the lung fields were quite conspicuous, though compatible with normal. (4) Serum chloride determinations gave results well above upper limits of normal: 111, 115.5, 113, 119 meq./ L.; CO_2 combining powers were low: 35.7, 41.9, 27.1, 39, 34.7 vol. per cent (venous blood determinations). (5) A number of other tests are not reported here. Angiocardiography, heart catheterization, and pulmonary function tests could not be performed, as the final complication and death of the patient did not allow us to complete the investigative program.

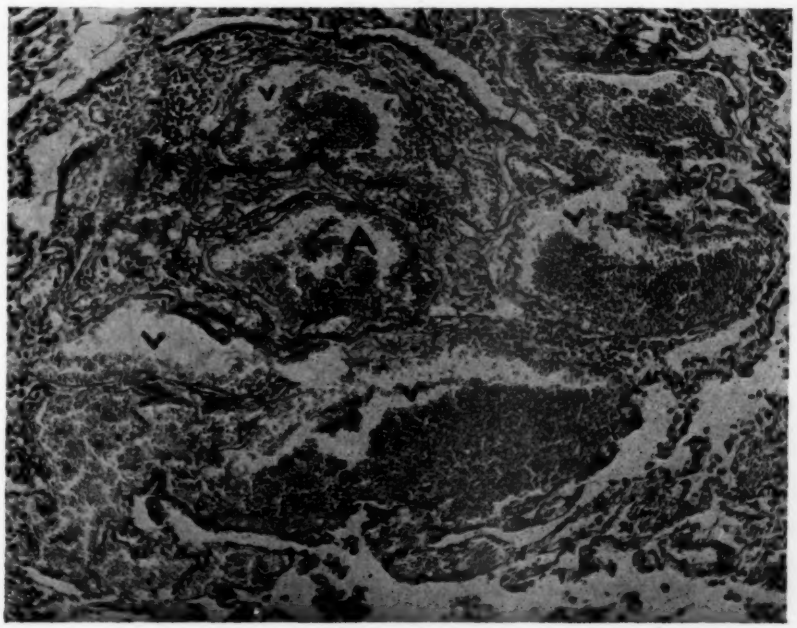

Fig. 6.—Case 2. Near the center there is a small pulmonary artery (*A*) with scarred wall, surrounded by conspicuous congested veins (*V*). Through serial sections a communication between the arterial lumen (*A*) and a venous one (*V*) was detected. Bronchiolar epithelium can be seen near the upper margin. (Hematoxylin and eosin stain; ×91.)

Necropsy.—Cadaver weighed 40 Kg. and was 168 cm. in height. There was a splenectomy scar. Slight conjunctival jaundice was present. The heart, weighing 250 grams, presented only slight hypertrophy and dilatation of the right ventricle. The lungs showed rare fibrous adhesions to the chest wall and small hydrothorax at the right (200 ml. of fluid). The right lung (400 grams) presented partial collapse and the left one (280 grams) areas of acute compensatory emphysema. The liver gave the picture of schistosomal cirrhosis, involving in the process the large and small portal spaces. Recent occlusive thrombosis of the portal, splenic, and mesenteric veins, causing hemorrhagic infarction of the distal ileum (30 cm. in length) and serofibrinous peritonitis (about

600 ml. of fluid in the abdominal cavity). The esophagus showed, at its inferior third, varices which were not conspicuous. Kidneys did not show changes. The brain (1,360 grams) was edematous.

Microscopic Examination.—The lungs (sections from 3 blocks) presented very rare schistosomal granulomas or their scars. There were arterial changes caused by schistosome ova similar to those in Case 1, although less frequent. The arteriovenous fistulas were less common, 9 fistulas being found in a section 6 μ thick and in an area of 2 sq. cm. However, a few arterioles and precapillaries showed a fibrous intimal thickening with lumen narrowing. Occasional serous endarteritis and hyaline thrombosis were seen. The picture of arterial lumen division (organized thrombus) was very rare. The basal membrane of the pulmonary capillaries presented no thickening. The right lung presented areas of collapse and the left lung areas of alveolar emphysema. The heart (left ventricle) was normal histologically. Liver showed schistosomal cirrhosis and chronic passive hyperemia.

DISCUSSION

These 2 cases of Manson's schistosomiasis were in the stage of hepatic cirrhosis with portal vein hypertension. Through anastomoses linking portal and systemic venous territories, *Schistosoma mansoni* ova and/or worms could get from the portal system to the lungs. In the latter there appeared vascular changes caused by the direct action of the ova (granulomas and their scars) and lesions not directly related to eggs (mainly a pulmonary endarteritis), as previously described.[5,6] These latter changes were more evident in one case (M. F. B.), probably causing in this patient a narrowing of the pulmonary arterial tree and consequent slight hypertrophy and dilatation of the right ventricle, due to pulmonary hypertension. In the other patient (J. Z. R.), the pulmonary artery changes were not important enough to cause hypertension, as indicated by the normal right ventricle found at necropsy, as well as by the normal pressure figures obtained at catheterization.

Through the necrotizing action of schistosome ova on small pulmonary branches (between 40 and 200 μ in diameter) and adjacent pulmonary venules, frequent arteriovenous fistulas were formed in both patients (Figs. 4-6). Such fistulas must be responsible for the marked cyanosis observed in such patients as these, in whom no other anatomic or functional basis for arterial blood unsaturation can be demonstrated either clinically or at necropsy. In this regard, even in Case 2, in which some heart strain was found, there were no indications that this incipient "cor pulmonale" was the chief basis for the cyanosis of the patient. A much more satisfactory explanation was the shunting of venous blood through the numerous arteriovenous fistulas.

Arteriovenous anastomoses through "Sperrarterien," as described by von Hayek[10] in normal lungs, were not found in these cases.

The very thin walls of the pulmonary venules, surrounded by pulmonary alveoli (Fig. 5) may reasonably explain the good arterial saturation obtainable after inhalation of oxygen, as observed in both patients. In other words, the A-V fistula walls could function as normal alveolar walls as far as gaseous exchanges are concerned when a higher oxygen tension is provided at the terminal air passages. This very interesting phenomenon will be studied in future cases, in order to find out if this seemingly logical explanation is the real one.

The angiocardiographic aspect observed in Case 1 is quite unique in our experience (Fig. 3). The granular aspect which appears in the early plates and

persists up to 9.6 seconds after injection is quite striking, when one considers that normally at 8 seconds both left atrium and left ventricle should have been cleared of contrast. To what extent this fact, as yet not explained, may be considered a diagnostic or even pathognomonic feature in these cases, only our and others' future experience will be able to disclose.

Rather curious laboratory findings in our cases are high chloride plasma levels with low CO_2 combining powers. These findings, present in both cases and for a number of times, have not as yet been explained as far as their pathogenesis is concerned. We have no elements even to tell which deviation should be considered as being primary, but at least we can say that no evidence of chronic hyperventilation was present in our patients. Cohn and associates[3,4] have shown that oxygen consumption in animals is low in the presence of low chloride concentrations; it was suggested that the chloride ion may be involved in the transport of oxygen from the blood to the tissues. If this observation is valid for man, one is tempted to interpret the high chloride concentrations in our cyanotic patients as a possible adaptation mechanism permitting the organism to get as much as possible from the available oxygen in the peripheral blood.

It is quite clear, then, that more complete studies are needed in similar cases, in order to clarify some of the features presented by patients with this syndrome, as well as to enable one to recognize those cases and separate them from the possibly more common group of schistosomal "cor pulmonale." We hope to be able to report on our additional experience in the near future.

SUMMARY AND CONCLUSIONS

In 2 cases of pulmonary schistosomiasis in which marked cyanosis and clubbing of fingers were prominent manifestations, the presence of numerous arteriovenous fistulas in the lungs is described. These fistulas were produced by schistosome ova which reach the small pulmonary vessels. In one of the patients no evidence of schistosomatic "cor pulmonale" was found, and, in the other, although this condition was present, it was in its early stages and could not account for the clinical and laboratory picture.

From the clinical, laboratory, and anatomopathologic studies done, it is concluded that those fistulas may be the major factor in the genesis of the marked cyanosis presented by some patients with schistosomiasis and cannot be explained entirely on the basis of a chronic "cor pulmonale."

In our cases an electrolyte pattern of low CO_2 combining power and high chloride plasma level was noticed, and additional studies will try to disclose its causative mechanism. Angiocardiography in 1 patient revealed a peculiar "lacework" aspect of the pulmonary vessels, as well as a persistence of contrast in the lungs beyond normal.

The fact that 3 other patients in whom this condition is probably present are now under study in our Service suggests that such cases are not at all rare and the number of those diagnosed during life should increase when medical personnel becomes aware of its existence.

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DIAGNOSIS OF CENTRAL SHUNTS FROM ABNORMALITIES OF PERIPHERAL DYE DILUTION CURVES

CURT A. WIEDERHIELM, AND ROBERT A. BRUCE, M.D.

SEATTLE, WASH.

WITH THE ASSISTANCE OF CHARLOTTE HAMILTON, AND RICHARD PARKER

CENTRAL shunts in patients with congenital heart disease distort indicator dilution curves. Acyanotic patients with predominantly left-to-right shunts exhibit curves with low maximal concentration and delayed clearance of the indicator from the pulmonary vascular bed.[1] Cyanotic patients with predominantly right-to-left shunts exhibit curves with secondary deflections on the upslope limb, earlier appearance and prolonged build-up time.[2] Patients without shunts who have low cardiac output exhibit curves with delayed appearance and clearance of the indicator, and also prolonged build-up time.[1] In the last group the 3 time components increase proportionally, suggesting a simple method to detect central shunts. It is the purpose of this paper to describe a method for quantitative analysis of time relationships of indicator dilution curves from cardiac patients with and without shunts.

MATERIAL

Fifteen normal adult subjects and 80 patients with heart disease comprise the material in this study. There were 58 patients with rheumatic, atherosclerotic, or hypertensive heart disease, or high output states who had no central shunts. Twenty-two patients with congenital mal formations were subdivided into 3 categories according to the direction of the predominant shunt as determined by cardiac catheterization. The categories were (a) "left-to-right shunts"—when this was at least 3 times greater than right-to-left values, (b) "right-to-left shunts"—when this was at least 3 times greater than left-to-right values, and (c) "bidirectional shunts"—when neither predominated, i.e., when the values were intermediate between the limits specified for (a) and (b).

METHODS

Hemodynamic evaluation of shunting was determined on the basis of the following modifications of the Fick principle[3]:

$$\text{Total pulmonary flow} = Q_{TP} = \frac{\dot{V}_{O_2}}{C_{PV} - C_{PA}}$$

$$\text{Effective pulmonary flow} = Q_{EP} = \frac{\dot{V}_{O_2}}{C_{PV} - C_{VC}}$$

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$$\text{Systemic flow} = Q_S = \frac{\dot{V}_{O_2}}{C_{FA} - C_{VC}}$$

$$L \rightarrow R \text{ Flow} = Q_{LR} = Q_{TP} - Q_{EP}$$

$$R \rightarrow L \text{ Flow} = Q_{RL} = Q_S - Q_{EP}$$

Where $\dot{V}_{O_2}$ = oxygen consumption and C = oxygen content of blood from pulmonary veins (PV), pulmonary artery (PA), average of venae cavae (VC), and femoral artery (FA).

The left-to-right and right-to-left shunt flows were expressed as percentages of total pulmonary and systemic flows, respectively.

All indicator dilution curves were recorded with Wood's oximeter earpiece on a 10-inch Leeds-Northrup strip chart recorder, using an amplifier system with linear response characteristics.[4] In each instance the earpiece was carefully applied to the pinna of the recumbent subject, and 15 minutes were allowed to elapse in order to assure arterialization of the capillary bed. Four milliliters of 0.5 per cent Evans blue solution were injected rapidly from a calibrated syringe and needle into an antecubital vein and the arm was promptly raised to prevent pooling of the dye at the site of injection. Since the arm was maintained in a dependent position prior to the njection, elevation of the arm released the pooled blood in the distal veins and assured rapid passage of the dye bolus into the superior vena cava.

The following circulation time intervals were obtained from the time concentration curves.

1. *Appearance time* (*A*) was defined as the time interval from the beginning of injection to the first appearance of indicator at the sampling site (Fig. 1).

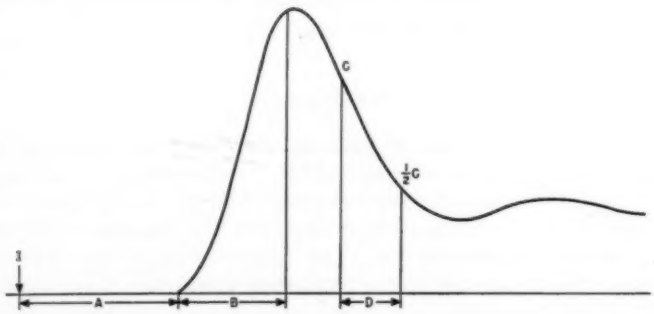

Fig. 1.—Definition of appearance time (*A*), build-up time (*B*), and derivation of the "disappearance time constant" (*D*), in a typical normal indicator dilution curve.

2. *Build-up time* (*B*) was defined as the time interval from the beginning of the upslope to the peak deflection (Fig. 1).

3. *Disappearance time constant* (*D*) was derived by arbitrarily selecting a point on the exponential portion of the downslope limb and measuring the time required for a fall in concentration to one half of its original value (Fig. 1). This time value defines the slope of the downslope limb.

The time values were expressed in the form of ratios (B/A and D/A), to minimize the effect of variations in cardiac output.

RESULTS

1. *Circulation Times and Ratios in Absence of Shunting.*—

The means and ranges of the time intervals A, B, D and circulation time

ratios B/A and D/A are presented in Table I for 15 normal subjects and for 58 patients with various types of heart disease without shunts. Although the mean appearance time (A) was significantly longer ($P<.007$) for the cardiac patients than for the normal subjects, there were no differences between the means of the B/A or D/A ratios of these 2 groups. The cardiac output ranged from 1.4 to 12.9 L. per minute for all these patients. Thus, there is no significant change in circulation time ratios over the usual range of resting values for blood flow.

2. *Circulation Times and Ratios in Presence of Shunting.—*

a. *Predominantly left-to-right shunts:* Patients with predominantly left-to-right shunts exhibit slightly shorter appearance time (A) than normal subjects (Fig. 2). This is attributed to the high output state within the pulmonary circuit, which is characteristic of these lesions. The B/A ratio also tends to be slightly higher than in normal subjects, but neither of these changes is of sufficient magnitude to be significant statistically. However, the mean of the D/A ratio is significantly increased ($P<.001$), although normal values may be obtained in patients with shunt flow less than 30 per cent of total pulmonary blood flow.

b. *Predominantly right-to-left shunts:* Patients with predominantly right-to-left shunts exhibit the shortest appearance time (A) (Fig. 2), although the maximal value for this group overlaps the minimal value for either normal subjects or cardiac patients without shunts (Table I). Similarly, the B/A ratio is usually significantly elevated. The circulation time ratio D/A is also increased somewhat, but not so markedly as for patients with predominantly left-to-right shunts.

These patients also exhibit the typical manifestations of right-to-left shunts,

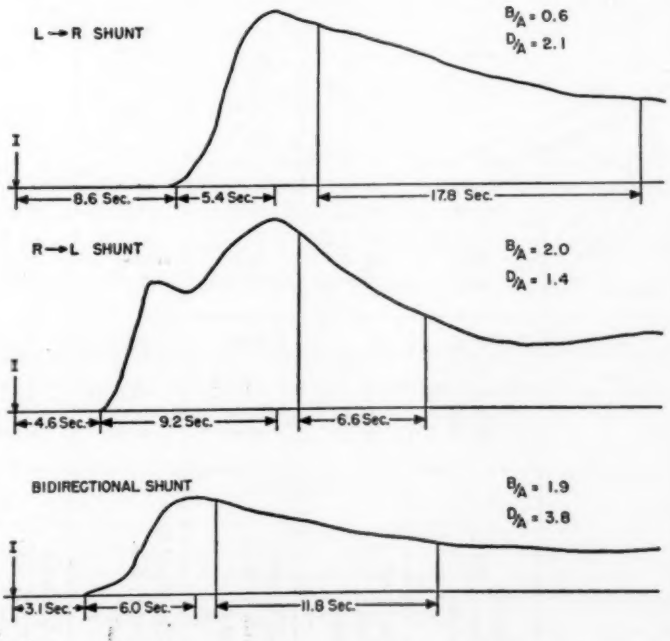

Fig. 2.—Dilution curves obtained in patients with central shunts. For full explanation, see text.

TABLE I

	A	B	D	B/A	D/A	% SHUNT FLOW		HEMOGLOBIN (GRAMS %)	ARTERIAL SAT., %
						R–L	L–R		
Normals									
Mean ± S.D.	10.4 ± 2.9	6.8 ± 1.6	4.7 ± 1.4	0.7 ± 0.2	0.5 ± 0.1	———	———	———	97 ± 1
Range	7.2 — 18.0	5.2 — 11.2	3.2 — 7.6	0.5 — 1.0	0.3 — 0.8	———	———	———	95 — 98
n	15	15	15	15	15	———	———	———	15
Non-Shunt									
Mean ± S.D.	13.1 ± 5	9.8 ± 4.5	7.2 ± 4.9	0.7 ± 0.2	0.5 ± 0.2	———	———	———	96 ± 2
Range	5.2 — 29	4.0 — 25.2	2.8 — 26.0	0.5 — 1.3	0.3 — 1.3	———	———	———	91 — 98
n	58	58	58	58	58	———	———	———	30
L–R Shunts									
Mean ± S.D.	8.2 ± 2.5	7.8 ± 2.7	20.3 ± 13	1.0 ± 0.4	2.7 ± 1.6	7.1 ± 5.7	50.4 ± 18	13.2 ± 1.5	95 ± 2
Range	3.4 — 11.8	5.2 — 12	5.0 — 49.0	0.6 — 1.6	0.6 — 6.5	0 — 19	22 — 78	10.8 — 16.5	91 — 98
n	11	11	11	11	11	11	11	11	11
Bidirectional Shunts									
Mean ± S.D.	8.2 ± 3.0	8.0 ± 3.4	16.1 ± 8.9	1.1 ± .5	2.1 ± 1.1	25 ± 11	36 ± 9	14.0 ± 2.0	91 ± 3
Range	3.5 — 12.6	4.3 — 12.8	6.5 — 30.0	0.7 — 1.7	1.0 — 3.4	18 — 44	20 — 44	10.8 — 18.1	86 — 94
n	6	6	6	6	6	6	6	6	6
R–L Shunts									
Mean ± S.D.	5.4 ± 2.8	12.2 ± 4.8	9.0 ± 5.4	2.8 ± 1.9	1.7 ± 1.2	48 ± 22	7 ± 7	18.4 ± 2.7	78 ± 10
Range	2.4 — 9.6	8.2 — 20.2	4.7 — 16.4	1.1 — 5.9	0.9 — 3.9	18 — 80	0 — 15	14.5 — 21.6	66 — 93
n	5	5	5	5	5	5	5	5	5

namely, desaturation of arterial blood and compensatory polycythemia (Table I). Hence, the reliable detection of right-to-left shunts is based upon the combination of cyanosis, polycythemia, shortened appearance time (A), and increased circulation time ratio B/A.

c. *Bidirectional shunts:* Patients with bidirectional shunts in whom neither direction predominates exhibit intermediate values (Fig. 2) as indicated in Table I. Thus, the appearance time (A) is shortened, the circulation time ratios B/A and D/A are both increased somewhat, there is only slight desaturation of arterial blood and usually no polycythemia. Because of the small and variable changes, bidirectional shunts are less reliably recognized by these criteria. Nevertheless, minor deviations in these characteristics beyond the normal range should make one suspect the possibility of bidirectional shunts, especially if the physical examination reveals findings compatible with congenital malformations of the heart.

DISCUSSION

Prior to making definitive studies such as cardiac catheterization and/or angiocardiography, the use of indicator dilution curves provides a simple screening test for determining the presence of significant central shunts. In view of the findings reported here, it is obvious that the main value of this technique is for the detection of left-to-right shunts in acyanotic patients with heart murmurs. The method is useful in establishing a differential diagnosis between organic and functional murmurs in patients with systolic murmurs and some accentuation of the second sound in the pulmonic area, radiographic evidence of slight to moderate enlargement of the right heart, and prominence of the pulmonary vasculature. In apprehensive patients with a functional systolic murmur along the left sternal border, the indicator dilution curve may not only exclude a shunt, but also reveal a high output state.

SUMMARY

1. Circulation time values for appearance (A), build-up (B), and disappearance (D) of indicator dilution curves have been defined and determined for normal subjects and cardiac patients with and without central shunts.

2. Circulation time ratios B/A and D/A were relatively independent of variations in cardiac output, but changed significantly in the presence of central shunts.

3. Significant increases in circulation time ratio D/A were usually observed in acyanotic patients with predominant left-to-right shunts. The value of this technique as a screening procedure has been discussed.

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VENTRICULAR SEPTAL DEFECT: A CORRELATIVE CLINICAL AND PHYSIOLOGIC STUDY OF FIFTY CASES

THEODORE F. HUBBARD, M.D., WILLIAM D. ANGLE, M.D., AND B. J. KOSZEWSKI, M.D.

OMAHA, NEB.

THIS paper reviews the clinical and physiologic data from 50 patients with isolated ventricular septal defect who underwent cardiac catheterization. An attempt is made to correlate the clinical, electrocardiographic, and fluoroscopic findings with the physiologic data in these cases. The spectrum of cases presented also allows consideration of some of the dynamic factors involved in determination of the direction and magnitude of shunt in ventricular septal defect.

MATERIALS AND METHODS

The cases were selected from the records of patients catheterized during the past 3 years. The heart catheterization studies were carried out according to standard techniques and one or more of the authors personally had studied each case clinically. In those cases with significant left-to-right shunts the diagnosis was established by the observation of a significant gradient in oxygen saturation between the right atrium and right ventricle. In those cases with mixed shunts or pure right-to-left shunts the presence and location of the defect were confirmed by passing the catheter through the defect, by intracardiac dye dilution curves,[1] or by angiocardiography. In none of the cases selected did the catheterization data suggest any associated malformation other than perhaps some abnormality in the location of the aortic root in a few of the cases, dextrocardia in one case, and evidence of dynamic aortic insufficiency in a few of the cases.

Included in this series were many cases which would be considered as examples of the Eisenmenger syndrome in that they exhibited continuous or intermittent arterial oxygen unsaturation. These were included in the study since by either clinical or physiologic criteria we did not find them sharply set apart from cases with similar hemodynamic alterations without arterial unsaturation. In addition, we had one case which was hemodynamically very different from the usual Eisenmenger syndrome but which showed a marked bidirectional shunt.

Since in the infants and small children it was not possible to obtain reliable steady-state oxygen consumption studies, the shunts were calculated in relative rather than absolute terms assuming the oxygen saturation of pulmonary venous blood to be 98 per cent.

RESULTS

Table I summarizes the essential clinical and physiologic data in these 50 cases. The cases are arranged in ascending order of the ratio of right ventricular systolic pressure to the systemic systolic pressure. The patients ranged in age from 4 months to 45 years and were about equally divided between the sexes.

From the Departments of Medicine of Bishop Clarkson Memorial Hospital and The University of Nebraska College of Medicine.

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Easy fatigability and exertional dyspnea both were present in approximately half of the cases, and these symptoms correlated with increasing pulmonary artery and right ventricular systolic pressures, as well as with increasing right ventricular end-diastolic pressures.

Frequent upper and lower respiratory infections occurred in 21 of the cases. This complication was particularly common in the cases with large left-to-right shunts and usually occurred during the period of infancy and early childhood. Although none of the cases showed definite clinical evidence of frank congestive heart failure at the time of the catheterization, several of the patients with pulmonary hypertension gave histories suggesting previous left and/or right ventricular failure. A history of continuous or intermittent cyanosis was obtained in 21 cases. All but 3 of these showed clubbing of the digits. In 15 of these cases and in 1 additional case there was arterial oxygen unsaturation at rest.

Physical examination disclosed some degree of left chest wall deformity in the majority of cases. Cardiomegaly by physical examination as a rule was present only in those cases with right ventricular hypertension, particularly when there was an associated large left-to-right shunt. Those cases with moderate or marked right ventricular and pulmonary artery hypertension manifested a precordial heave and an increase in the pulmonic second sound which correlated well with the degree of hypertension. Slight or no increase in the splitting of the second sound in the pulmonary area was noted in most cases. In those cases with a large left-to-right shunt and little elevation of the pulmonary artery pressure, a prominent apex thrust usually was observed.

In the majority of cases a murmur of Grade 3 to 4 intensity (on the basis of 4 grades) accompanied by a thrill was located at the third or fourth intercostal space near the left sternal border. Being of great intensity, the murmur was often widely transmitted. When the absolute volume of left-to-right shunt was small, the murmurs were often of less intensity. The murmur was of least intensity in 3 patients in whom there was marked pulmonary hypertension and little shunt flow in either direction. An early diastolic blowing murmur in the pulmonary area was heard in 11 of the cases with pulmonary hypertension. In 2 cases with large left-to-right shunts there was an apical mid-diastolic murmur.

Electrocardiographically, most of the cases with normal or slightly elevated right ventricular pressure showed mild or moderate left ventricular hypertrophy which correlated to a low degree with the volume of left-to-right shunt. In addition, these cases frequently showed a pattern of large diphasic QRS complexes in the midprecordial leads. The cases with moderate or marked right ventricular hypertension also frequently showed this pattern of large diphasic QRS complexes in the midprecordial leads. Electrocardiographically, right ventricular hypertrophy of the concentric type was present in all the cases with moderate or marked right ventricular hypertension, except for 1 case which showed an incomplete right bundle branch block, and 1 case which showed right bundle branch block. Concentric right ventricular hypertrophy was evidenced generally by a swing of the mean spatial QRS vector to the right and anteriorly, and by the presence of an abnormally large Rs, qR, or R with a slurred or notched upstroke in V_1 accompanied by a delay in the intrinsicoid deflection in V_1. Three additional

TABLE I. SUMMARY OF THE CLINICAL AND CATHETERIZATION FINDINGS IN 50 CASES OF VENTRICULAR SEPTAL DEFECT

CASE NUMBER	AGE	RATIO OF RIGHT VENTRICULAR SYSTOLIC PRESSURE TO SYSTEMIC SYSTOLIC PRESSURE	RIGHT VENTRICULAR PRESSURE	SYSTEMIC ARTERIAL PRESSURE	LEFT-TO-RIGHT SHUNT (% OF TOTAL PULMONARY FLOW)	RIGHT-TO-LEFT SHUNT (% OF TOTAL SYSTEMIC FLOW)	SYMPTOMS				CARDIAC SIGNS				ECG FINDINGS				ROENTGENOLOGIC FINDINGS				
							FATIGUE	DYSPNEA	RESPIRATORY INFECTIONS	CYANOSIS	PRECORDIAL LIFT	SYSTOLIC MURMUR	DIASTOLIC MURMUR	PULMONARY SECOND SOUND	LEFT VENTRICULAR HYPERTROPHY	RIGHT VENTRICULAR HYPERTROPHY	LARGE DIPHASIC QRS COMPLEXES	LEFT VENTRICULAR HYPERTROPHY	RIGHT VENTRICULAR HYPERTROPHY	PULMONARY TRUNK ENLARGEMENT	HILAR VASCULARITY	HILAR VASCULAR PULSATIONS
1	26	0.17	16/2	90/54	30	0		+				+++			++	*						
2	6	0.20	20/4	104/64	29	0	+			+	+	++			++		++	++		+		+
3	3	0.21	20/5	92/60	60	0			++			++		+	++		++	++		+	+	
4	14	0.22	24/4	110/80	35	0						+++						+		+	+	+
5	12	0.23	25/5	110/80	38	0						+++									++	+
6	4	0.24	22/5	90/64	54	0			+			++		+	++		++	+	+	+	+	+
7	6	0.24	25/5	105/70	25	0						+++			+		+			+	+	+
8	10	0.25	26/5	105/65	54	0		+	++			+++		+	++		++			+	+	+
9	4	0.26	25/3	95/50	31	0	+					++		+	+					+	+	+
10	11	0.27	27/5	100/75	50	0	+	+	+			+++		+	+					+	++	++
11	13	0.32	38/8	108/68	27	0	+					+++		+	+					+	++	++
12	13	0.34	42/5	125/64	53	0	++					+++		+		*		+		+	+	+
13	13	0.35	35/3	100/70	43	0						+++		+	++			+		+	+	++
14	5	0.38	35/5	90/60	30	0						+++			+					+	+	+
15	2	0.39	35/5	90/60	57	0			+			++++		+	++		+	+			+++	+

| | | |

TABLE I. SUMMARY OF THE CLINICAL AND CATHETERIZATION FINDINGS IN 50 CASES OF VENTRICULAR SEPTAL DEFECT—CONT'D

CASE NUMBER	AGE	RATIO OF RIGHT VENTRICULAR SYSTOLIC PRESSURE TO SYSTEMIC SYSTOLIC PRESSURE	RIGHT VENTRICULAR PRESSURE	SYSTEMIC ARTERIAL PRESSURE	LEFT-TO-RIGHT SHUNT (% OF TOTAL PULMONARY FLOW)	RIGHT-TO-LEFT SHUNT (% OF TOTAL SYSTEMIC FLOW)	SYMPTOMS				CARDIAC SIGNS				ECG FINDINGS			ROENTGENOLOGIC FINDINGS				
							FATIGUE	DYSPNEA	RESPIRATORY INFECTIONS	CYANOSIS	PRECORDIAL LIFT	SYSTOLIC MURMUR	DIASTOLIC MURMUR	PULMONARY SECOND SOUND	LEFT VENTRICULAR HYPERTROPHY	RIGHT VENTRICULAR HYPERTROPHY	LARGE DIPHASIC QRS COMPLEXES	LEFT VENTRICULAR HYPERTROPHY	RIGHT VENTRICULAR HYPERTROPHY	PULMONARY TRUNK ENLARGEMENT	HILAR VASCULARITY	HILAR VASCULAR PULSATIONS
38	6	0.95	95/8	100/60	30	0	+	+			++	++		+++	++	+++	++	+	++	++	+	+
39	10	0.96	112/6	116/70	20	25	+	++		++	++	++	+	+++		+++			+++	++	++	
40	15	0.97	112/8	115/76	32	10	++	++	++	+	++	+++	+	++	+	+++	+	+	++	++	++	++
41	6 mo.	0.99	84/0	85/50	75	15		++	+++	+	++	+++	+	+++	++	++	++	++	++	++	+++	+++
42	10	0.99	122/7	123/78	20	40	++	++		+++	++	+		+++		+++	++	++	++	++	++	++
43	29	1.00	125/5	125/80	10	20	+	+		++	++	+++		++		+++			++	++	+	+
44	45	1.00	115/5	115/80	10	10	+	+		+	++	+		+++		+++			++	++	++	
45	4 mo.	1.02	87/4	85/50	67	30		+++	+++	++	+++	+++		+++	++	++	++++	++	++	++	+++	+++
46	37	1.03	113/8	110/70	36	33	++	++		+++	++	+++	+	++		+++	++		++	+++	++	+
47	11	1.04	115/10	110/75	53	8	+	++		+	++	+++	++	+++	+	+++	++	+	++	++	++	++
48	7	1.03	114/6	110/70	0	27	+	++		++	+++	++	+	++		+++			++	++	++	
49	4	1.10	110/8	100/60	0	5	+	++		+	++	+		+++		++			++	++	++	++
50	4	1.10	110/8	100/65	0	10	+	+		+	++	+		+++		+++	++		++	++	++	+

*Incomplete Right Bundle Branch Block.
†Complete Right Bundle Branch Block.

patients showed the incomplete right bundle branch block pattern as manifested by an RSR′ in V_1 of less than 0.12 second duration. The pattern of diastolic overloading of the left ventricle[2] was seen in a few of the cases with moderate left-to-right shunts without significant pulmonary hypertension.

In those cases with marked pulmonary hypertension and right-to-left shunts there was often electrocardiographic evidence of right atrial hypertrophy as manifested by a tall or peaked P wave in Leads II or III and V_1. In 3 of the patients with large left-to-right shunts a *P mitrale* pattern was present.

Fluoroscopically, the presence of a moderate to large left-to-right shunt usually was associated with evidence of left ventricular hypertrophy, some increase in the size of the pulmonary trunk, and increased hilar vascular pulsations. The latter finding usually correlated well with the volume of left-to-right shunt, but in a few of the patients with marked pulmonary hypertension and small left-to-right shunts a significant increase in hilar pulsations was apparent. Major degrees of pulmonary hypertension were manifest by right ventricular hypertrophy, further increase in the size of the pulmonary trunk and in the width of the right and left main pulmonary arteries and their inferior branches. When in the presence of marked pulmonary hypertension there was little or no left-to-right shunt, there was a relative decrease in the peripheral lung field vascularity.

The cardiac catheterization studies showed that only 11 of the patients in the series had normal pulmonary artery pressures. In 27 cases the right ventricular systolic pressure was equal to 50 per cent or more of the systemic sytolic pressure, and in 22 cases equal to 80 per cent or more. The volume of left-to-right shunt varied from zero to 78 per cent of the total pulmonary flow, with 23 of the patients having shunt volumes of 50 per cent or more. In general, there was no systematic relationship between the volume of left-to-right shunt and the degree of elevation of pulmonary artery pressure.

Right-to-left shunt with one exception was uniformly associated with right ventricular systolic pressures approximately equal to systemic pressures. Nineteen of the patients showed evidence of a right-to-left shunt under resting conditions. In a few of these patients the shunt volume was too small to produce arterial oxygen unsaturation (below 93 per cent) and could be identified only by a small early appearance "hump" on the buildup limb of the dye dilution curve. Several additional patients showed evidence of a right-to-left shunt only with exercise. Most of the patients with resting arterial oxygen unsaturation were polycythemic.

In several of the patients with marked pulmonary hypertension, there were "a" waves in the right atrial pressure tracing of increased amplitude, and a systematic tendency for slight increases in the right ventricular end-diastolic pressures and right atrial mean pressures. The systemic arterial pulse wave tracing gave evidence of dynamic aortic insufficiency in several of the patients. The pulmonary "wedge" pressure was normal in those cases in which it was measured. In 8 of the patients the catheter tip passed easily into the aorta from the right ventricle; there was evidence of right-to-left shunt in all of these cases.

DISCUSSION

Symptoms in patients with ventricular septal defect correlated well with the degree of dynamic abnormality. The patients without pulmonary hypertension seemed to tolerate the lesion with few symptoms, except for the frequently recurring respiratory infections in children with large left-to-right shunts. Major degrees of exertional dyspnea and disability tended to increase with increasing pulmonary artery pressure.

Physical examination, electrocardiography, and fluoroscopy usually permitted proper diagnosis and fairly accurate prediction of the degree of dynamic abnormalities. The murmur is usually the most distinctive physical finding. It is usually harsh, of Grade 3 to 4 intensity, associated with a thrill, and located maximally along the lower left sternal border. Its intensity is in part a function of the absolute volume of left-to-right shunt and as such tends to be somewhat less intense in infancy and in those cases with a "balanced" circulation and little shunt. When the left-to-right shunt volume is large and there is little elevation of the pulmonary artery pressure, a prominent apex thrust may be noted and there is little increase in the pulmonary second sound. Wide splitting of P_2 as seen in atrial septal defect is rarely encountered in this condition. An apical mid-diastolic murmur is present in a few of the cases with large left-to-right shunt and may represent the development of turbulence with high flow across the mitral valve. In those cases with pulmonary hypertension there is a prominent left parasternal lift and a loud sharp pulmonary second sound. An early diastolic blowing murmur along the left sternal border was common in these patients. Apparently, this was due usually to relative pulmonic insufficiency, but on occasion represented a dynamic aortic insufficiency. When the right ventricular pressure approached the systemic, cyanosis was common.

Electrocardiographically, the pattern of large diphasic RS complexes in the midprecordial leads was seen in approximately half the cases. This pattern is assumed to indicate combined ventricular hypertrophy including the septum and is a pattern uncommonly seen with other conditions.[2,3] We have seen this pattern in cases of tetralogy of Fallot in whom a left-to-right shunt was created surgically, in some cases of patent ductus arteriosus with moderate pulmonary hypertension, and in combined mitral and aortic valve disease.

The cases with normal right ventricular pressure usually showed left ventricular hypertrophy which correlated to a low degree with the volume of left-to-right shunt. The cases with significant right ventricular hypertension showed a pattern of concentric right ventricular hypertrophy. The incomplete right bundle branch block type of right ventricular hypertrophy so commonly seen in atrial septal defect was present in only 4 cases in this series.

The electrocardiographic observations are similar to those reported by Sodi-Pallares and associates[2] in a study of 32 catheterized cases of ventricular septal defect. However, they observed left ventricular hypertrophy consistently in the cases with pulmonary hypertension and found little evidence of left ventricular hypertrophy in the absence of pulmonary hypertension. Our observations on left ventricular hypertrophy tended to be contrary to these. A more detailed

analysis of the electrocardiogram in ventricular septal defect will be presented in a subsequent communication.

Roentgenologic examination almost invariably revealed enlargement of the pulmonary trunk and an increase in the hilar shadows and hilar pulsations. In the cases with normal pulmonary artery pressure these changes apparently are due entirely to the left-to-right shunt, and the degree of these changes usually correlated well with the size of the shunt. Left ventricular enlargement usually was seen in these cases and again correlated with the size of the shunt. In the cases with pulmonary artery and right ventricular hypertension the enlargement of the pulmonary trunk and the increase in hilar shadows were more marked, due apparently to the additive effect of pulmonary hypertension. These cases also showed right ventricular enlargement which correlated with the degree of pulmonary hypertension. Left atrial enlargement was seen in a few of the cases with a large left-to-right shunt.

SOME DYNAMIC CONSIDERATIONS

Of these 50 cases, 25 showed evidence of a right-to-left shunt at catheterization or gave a history of previous intermittent cyanosis. These cases could be classified as examples of the Eisenmenger syndrome. All of the cases showing a left-to-right shunt at the time of catheterization, except Case 18, had moderate or marked right ventricular hypertension. The occurrence of a right-to-left shunt in this case despite normal right ventricular pressure raises the question of the determinants of the size and direction of shunt in ventricular septal defect.

Selzer[4] gave morphologic evidence that the most important determinant of symptoms and dynamics in ventricular septal defect is the size of the defect. He observed that pulmonary hypertension was invariably present in the Eisenmenger syndrome and that the size of the septal defect was significantly larger than in the usual ventricular septal defect. He considered overriding of the aorta to be a significant though not necessarily essential feature of the syndrome.

Edwards and Civin[5,6] indicated the importance of pulmonary vascular changes in the development of pulmonary hypertension and reversal of shunt flow, and they regarded the phenomenon as an adaptive mechanism in large defects to protect the pulmonary vascular bed from "flooding" or to maintain sufficient resistance in the lesser circuit to assure an adequate systemic flow by lessening the left-to-right shunt. Blount[7] stated that evolution of the Eisenmenger syndrome is simply the resultant of a large ventricular septal defect with secondary or occasionally primary changes in the pulmonary arterioles. He would seem to deny any consequence of overriding of the aorta. Katz and associates[8] presented catheterization data on 20 cases of the Eisenmenger syndrome, 16 of which showed systemic arterial unsaturation. They concluded from their studies that the presence of pulmonary hypertension was entirely "fortuitous."

Case 18 of our series presents an interesting contribution to the controversy. The patient was a 6-month-old infant, severely cyanotic from birth, who had failed to gain weight and exhibited almost continuous pulmonary congestion and left ventricular failure. At rest the systemic arterial oxygen saturation ranged from 40 to 65 per cent. There was marked pulmonary congestion and cardiac

enlargement. At catheterization the catheter passed easily from right ventricle into either pulmonary artery or aorta. The aorta was noted to originate from a region anterior to the normal site. There were large shunts in both directions with left-to-right shunt predominating. Notwithstanding, there was a normal pressure in the right ventricle and pulmonary artery. We can offer no explanation for the right-to-left shunt in this case other than overriding of the aorta. We suggest that the direction of momentum of the right ventricular stream, which is toward the outflow tract of the ventricle, is the influence permitting right-to-left shunt in the presence of overriding of the aorta despite the absence of right ventricular hypertension. Such a case is clearly an unusual phenomenon as we know of no similar case in the literature.

SUMMARY

The clinical and catheterization data of 50 cases of ventricular septal defect were presented. It is concluded that in general the clinical data permit not only the diagnosis but a reasonably accurate estimation of the dynamic abnormality. A case with a large right-to-left shunt despite normal right ventricular pressure was presented and discussed in relation to various theories and viewpoints on the determinants of shunts in ventricular septal defect.

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CLINICAL SIGNIFICANCE OF SERUM ENZYME ALTERATIONS ASSOCIATED WITH MYOCARDIAL INFARCTION

FELIX WRÓBLEWSKI, M.D.

NEW YORK, N. Y.

INTRODUCTION

MYOCARDIAL infarction is associated with alterations in the activity of serum glutamic-oxaloacetic transaminase (SGO-T)[1] and serum lactic dehydrogenase (SLD).[2] The impressive amount of these enzymes in cardiac tissue, contrasted with the relatively small amount of enzyme activity in an equivalent amount of serum, results in significant elevations of serum enzyme activity when the enzyme is released from necrotic cardiac tissue into the blood stream (Table I). Other cardiac tissue enzymes present in great enough concentrations in human heart muscle may be expected to be released into the circulation following myocardial infarction.[3] It is the purpose of this report to summarize the clinical significance of the alteration of SGO-T and SLD associated with myocardial infarction.*

TABLE I. COMPARISON OF GLUTAMIC-OXALOACETIC TRANSAMINASE AND LACTIC DEHYDROGENASE ACTIVITY OF NORMAL HUMAN TISSUES AND SERUM

NORMAL HUMAN TISSUE	(UNITS PER GRAM OF WET TISSUE)	
	GO-T	LD
Heart	155,500	221,600
Liver	142,400	94,700
Skeletal muscle	99,300	160,200
Kidney	90,900	281,800
Spleen	13,600	108,800
Lung	10,000	73,600
Pancreas	28,300	131,200
Serum	20	470

From the Division of Clinical Investigation, Sloan-Kettering Institute, and the Department of Medicine, Memorial Center for Cancer and Allied Diseases, New York, N. Y.

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*The serum enzyme alterations discussed have been observed in over 100 human cases of acute transmural myocardial infarction. Fifty of these individuals had serum determinations of both lactic dehydrogenase and glutamic-oxaloacetic transaminase activity, while the remainder had measurements of serum glutamic-oxaloacetic transaminase alone. The medical literature contains reference to the measurement of transaminase in myocardial infarction in well over 400 cases and to less than 100 cases in which lactic dehydrogenase activity was determined.

METHODS OF MEASUREMENT OF SERUM ENZYMES

Serum glutamic-oxaloacetic transaminase has been measured chromatographically,[1a] spectrophotometrically,[4] and colorimetrically.[5] The mean SGO-T activity as measured by paper chromatography and as expressed as micromoles per milliliter per hour of glutamate formed is 0.622 ± 0.191. Spectrophotometrically, the mean SGO-T activity of normal adult sera is 22.1 ± 6.8 units, with a range of normal 5 to 40 units. When determined colorimetrically, the mean SGO-T activity is 16.4 ± 8.4 units, with a range of normal of 4 to 40 units. The technical aspects of the chromatographic method relegate it primarily to investigative pursuits. The advantages of the spectrophotometric and colorimetric techniques make these two methods suitable for routine clinical use. Serum lactic dehydrogenase activity has been measured spectrophotometrically.[2] The mean activity of SLD in normal adult sera is 440 ± 120 units, with a normal range of 200 to 680 units. SGO-T and SLD are measured at approximately 25° to 28° C. and without regard to the fasting state.

Both serum enzymes are stable for at least 24 hours at 4° C., although SGO-T appears to be more stable at refrigerator temperature than SLD. The activity of the two enzymes is the same in serum and heparinized plasma. Although hemolysis of a slight degree influences SLD activity, only considerable hemolysis increased SGO-T activity.

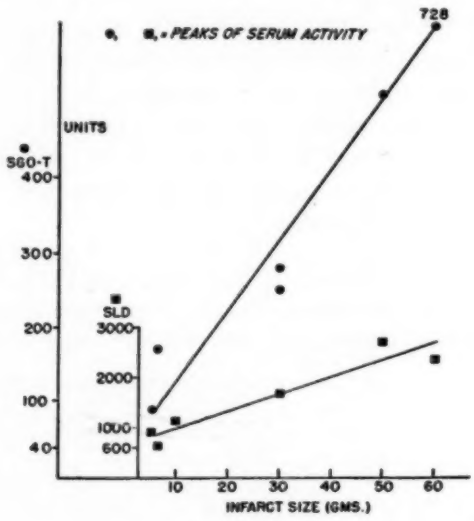

Fig. 1.—Correlation of peak SGO-T and SLD rise and estimated size of infarct following experimentally produced myocardial infarction in dogs.[6]

ALTERATIONS OF SERUM ENZYMES IN EXPERIMENTAL MYOCARDIAL INFARCTION

Alterations in SGO-T and SLD activity associated with myocardial infarction have been studied experimentally by coronary occlusion resulting from coronary artery ligation in the closed-chest dog. The changes in the two serum enzymes have been correlated with electrocardiographic, morphologic, and tissue enzyme content observations.[6] When the dogs succumbed to the experimentally produced infarction and/or were sacrificed at varying periods following coronary ligation, normal and infarcted cardiac tissues were assayed for glutamic-oxaloacetic (GO-T) and lactic dehydrogenase (LD) activity. A rough correlation exists between the peak SGO-T and SLD elevation, the duration of SGO-T and SLD rise, and the size of the infarct produced (Fig. 1). It was postulated that

the mechanism for SGO-T and SLD increase following experimental infarction was the leakage from infarcted muscle of GO-T and LD which found their way into the blood stream. This hypothesis rested on the observations that the infarcted muscle contained less GO-T and LD activity than adjacent normal cardiac tissue of the same animal, and that the older the infarct the less GO-T and LD activity was demonstrable in the necrotic tissue (Table II).

TABLE II. SGO-TRANSAMINASE ACTIVITY IN NORMAL AND INFARCTED HEART MUSCLE FOLLOWING EXPERIMENTAL MYOCARDIAL INFARCTION IN DOGS

NORMAL MUSCLE UNITS/GM.	INFARCTED MUSCLE UNITS/GM.	AGE OF INFARCT	RATIO OF $\frac{\text{NORMAL}}{\text{INFARCTED}}$
451,000	219,000	20 hr.	$\frac{2}{1}$
348,000	33,200	7 days	$\frac{20}{1}$
250,000	5,600	9 days	$\frac{45}{1}$

By the use of temporary occlusion of coronary arteries in dogs, myocardial ischemia of varying durations was produced, and the degree of ischemia correlated with electrocardiographic changes, SGO-T and SLD alterations, and heart tissue GO-T and LD activity.[7] With a few exceptions, myocardial ischemia in the presence of confirmatory electrocardiographic changes without histologic evidence of necrosis resulted in no significant elevation in the two serum enzymes' activities. However, when ischemia resulting from experimentally produced coronary insufficiency was prolonged enough to result in morphologic evidence of tissue necrosis, SGO-T and SLD were increased above the normal range. In dogs, experimental pericarditis was in most cases accompanied by no significant rise in SGO-T and SLD activity.[7b,8] A similar lack of changes in the two serum enzymes' activities was observed during the course of experimentally produced pulmonary infarction.[8]

ALTERATIONS OF SERUM ENZYMES IN CLINICAL MYOCARDIAL INFARCTION

Transmural myocardial infarction in the human adult is associated with a rise in SGO-T and SLD which becomes manifested approximately 6 to 12 hours after the estimated time of coronary occlusion. The rise in serum enzyme activities reach a peak within 24 to 48 hours, returning to the normal range by the fourth to the seventh day postinfarction (Figs. 2 and 3). It would appear that SGO-T activity returns to normal somewhat sooner than that observed for SLD (Fig. 4). The peak elevations noted following myocardial infarction are 2 to 15 times normal levels for SGO-T and 2 to 8 times for SLD. The peak rise

and duration of abnormal serum enzyme activities appear to be proportional to the size of the infarction and/or the degree of myocardial necrosis. This is in keeping with the experimental evidence in dogs, and the clinical observations that a poor prognosis is implied where SGO-T activity exceeds 300 units and SLD exceeds 3,500 units at their respective peak rise postinfarction. A small myocardial infarction, however, with slight tissue necrosis and a small rise in SGO-T

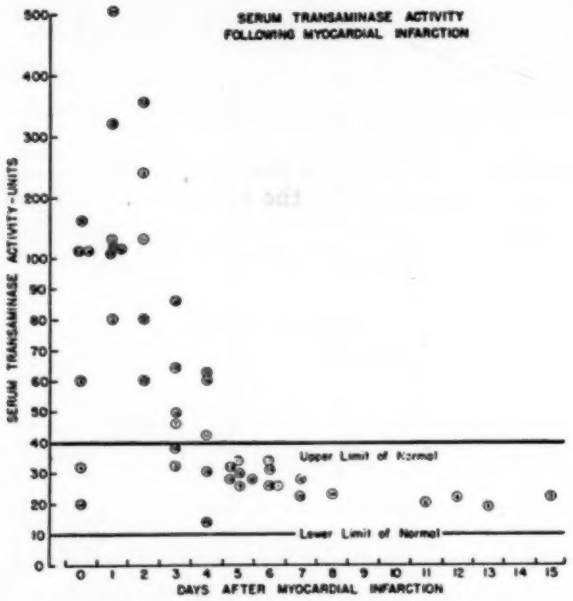

Fig. 2.—Values of SGO-T activity observed on various days in patients following acute myocardial infarction.

and SLD does not necessarily imply a favorable prognosis. Following myocardial infarction, the rise in SGO-T and SLD activity is not influenced by, nor correlated with, shock, blood pressure, heart failure, location of the infarction, anticoagulation, digitalis or its derivatives, quinidine, age, sex, color, body temperature, sedimentation rate, leukocyte count, or urinary output. The rise in SGO-T and SLD following infarction is not necessarily related to the configuration of the electrocardiogram. When the electrocardiogram is not diagnostic of, or is obscured by, previous myocardial infarction, bundle branch block, Wolff-Parkinson-White syndrome, or other electrocardiographic aberrations, the rise in SGO-T and SLD activity in a clinical setting suggestive of infarction is an especially helpful diagnostic tool. Secondary rises in SGO-T and SLD activity have been observed in patients who, following acute myocardial infarction, present clinical stigmata consistent with extension of the infarction.

Changes in SGO-T and SLD activity may contribute to delineating the process of myocardial necrosis in patients with substernal pain, not only with suspected coronary occlusion but also in the presence of coronary insufficiency without occlusion. It appears that SGO-T and SLD activity remain within normal limits in patients with status anginosis or coronary insufficiency, in spite

of accompanying transient ST-segment and T-wave abnormalities. When in these clinical settings of acute coronary insufficiency SGO-T and SLD activities are elevated, it is suggestive that ischemia of cardiac muscle has been accompanied and/or followed by myocardial necrosis.

In most cases of pericarditis of various causes, pulmonary emboli with and without pulmonary infarction, cardiac arrhythmias, and rheumatic carditis, no significant or consistent elevations in SGO-T and SLD activity have been observed.

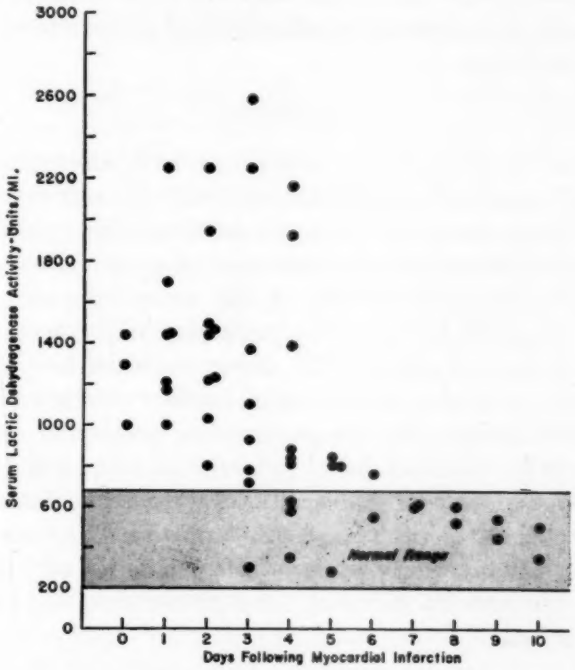

Fig. 3.—Values of SLD activity observed on various days in patients following acute myocardial infarction.

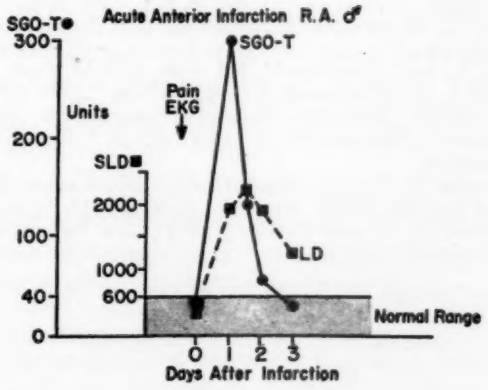

Fig. 4.—Comparison of SLD and SGO-T activity in a patient during the first 3 days following acute myocardial infarction.

ALTERATIONS OF SGO-T AND SLD ACTIVITY IN NONCARDIAC DISEASE STATES

In the absence of injury to the heart, liver,[9] and skeletal muscle tissue,[10] no significant alterations in SGO-T activity have been observed in neoplastic, allergic, infectious, congenital, degenerative, metabolic, and reactive or collagenous disease states. In addition to diseases associated with necrosis of the heart, liver, and skeletal muscle tissue, some instances of leukemia, disseminated carcinoma, and lymphoma cause elevations in SLD activity.[2] The quantitative and serial alterations in the two serum enzymes seen following acute myocardial infarction are usually not observed in other clinical states associated with elevated SGO-T and SLD activity.

SUMMARY

Acute myocardial infarction is associated with alterations in the activity of serum glutamic-oxaloacetic transaminase (SGO-T) and serum lactic dehydrogenase (SLD). These serum enzymes can be measured readily by simple techniques. From 6 to 12 hours following the onset of myocardial infarction there is a rise of 2 to 8 or 10 times the activity of the serum enzymes, with a maximum elevation within 24 to 48 hours. The peak rise in the serum enzymes is proportional to the extent of myocardial tissue necrosis, and the serum enzyme changes are thought to be due to the loss of cardiac muscle enzyme from necrotic tissue into the circulation. In the presence of equivocal electrocardiographic changes or tracings in which classical patterns of myocardial infarction are obscured, the rise in SGO-T and SLD activity in a clinical setting suggestive of infarction is an especially helpful diagnostic tool. The serum enzymes are altered in several other specific clinical settings but the serial and quantitative serum enzyme changes are usually different from those observed in association with myocardial infarction.

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DIAGNOSTIC AIDS IN ACUTE MYOCARDIAL INFARCTION: CLINICAL AND EXPERIMENTAL

SAMUEL LOSNER, M.D.,† BRUNO W. VOLK, M.D., AND STANLEY M. ARONSON, M.D.

BROOKLYN, N. Y.

THE definitive diagnosis of acute myocardial infarction in its early phase is a frequent clinical problem. No single method is available to the clinician to help him establish the existence of this lesion during the crucial interval before electrocardiographic and auscultatory findings become independently conclusive. Even after cardiac involvement has been ascertained clinically, the differentiation between coronary insufficiency, subendocardial or transmural infarction may remain in doubt. When serial electrocardiographic studies and clinical observations during the subsequent 2 to 5 days have proved the existence of a major occlusion in the coronary tree, the question of size of the affected area of myocardium still remains unresolved.

Previously, few laboratory methods such as the white blood count and erythrocyte sedimentation rate (ESR) were available as auxillary diagnostic aids for the recognition of acute coronary occlusion. The erratic or often misleading data obtained in many patients with these methods, however, frequently enhanced the dilemma for the clinician instead of assisting him in establishing the diagnosis. In previous publications, it was shown that the total white blood cell count is elevated only during the early phase of coronary occlusion, and that the ESR is frequently unreliable and far less indicative of the severity of the disease process than the maximum plasma fibrinogen concentration.[1,2] It has been demonstrated further that the ESR may be paradoxically depressed in patients with massive myocardial infarction.[3] In order to compensate for these deficits, a series of nonspecific laboratory procedures has been proposed recently as diagnostic aids in acute myocardial infarction. Such methods include serial studies of plasma fibrinogen concentration,[1] determinations of various enzymes, such as SGO-transaminase,[4,5] serum aldolase,[6,7] serum lactic dehydrogenase,[7,8] the C-reactive proteins,[9] serum mucoproteins,[10] serum polysaccharides,[11] serum copper,[12] as well as others.

The present study was inaugurated to evaluate the usefulness of a battery of laboratory tests (fibrinogen concentration, SGO-transaminase, serum aldolase, C-reactive protein, and erythrocyte sedimentation rate), as to the diagnosis and prognosis in patients with varying degrees of coronary inadequacy ranging

From the Isaac Albert Research Institute of The Jewish Chronic Disease Hospital, Brooklyn, N. Y.
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†Dr. Losner died on Jan. 14, 1957.

from transient coronary insufficiency to massive myocardial infarction, particularly when the tests were used simultaneously and in conjunction with serial electrocardiographic findings. These tests were selected because of the simplicity and sensitivity of the methods. In addition, these procedures were applied also to a series of dogs in which the left anterior descending coronary artery was ligated at various levels.

MATERIALS AND METHODS

1. *Clinical.*—In studies on 40 patients with acute myocardial infarction (including 15 cases diagnosed as coronary insufficiency and 10 patients with subendocardial necrosis), serial determinations of plasma fibrinogen concentration, SGO-transaminase, serum aldolase, C-reactive protein (CRP), and ESR were performed. The procedures were carried out daily during the first week, and, subsequently, on alternate days for periods up to 4 weeks. Electrocardiograms were taken at frequent intervals.

2. *Experimental.*—A group of 12 mongrel dogs, each weighing from 15 to 20 kilograms, was subjected to ligation of the descending branch of the left anterior coronary artery below the bifurcation of the main artery. This was considered a *high ligation.* In another series of 10 dogs a suture was placed just below the point where the septal artery branches off the descending ramus of the left anterior coronary artery. This was termed a *low ligation.* A third group of 10 animals, serving as controls, was subjected to a sham-operation, which was almost identical with the actual procedure, but which included only pericardiotomy. The coronary arteries were not violated. After intravenous sodium pentobarbital anesthesia in a dosage of 30 mg. per Kg., an endotracheal tube was inserted under laryngoscopic guidance and attached to a mechanical respirator. Under aseptic conditions the left side of the chest was explored through the fourth intercostal space, and the left atrium and the left coronary artery were adequately exposed. The ligatures were placed then at the described sites around both artery and vein.

Determinations of plasma fibrinogen concentration, SGO-transaminase, serum aldolase, the CRP, as well as the ESR, were carried out in all animals prior to operation and daily thereafter for at least 6 consecutive days. All animals were sacrificed between the sixth and the tenth postoperative day, and the hearts were examined grossly and microscopically to substantiate the occlusion of the vessels and resultant myocardial damage.

The fibrinogen concentration was determined by the clot density method.[13] The SGO-transaminase was estimated according to the procedure of Karmen, Wroblewski, and LaDue.[14] The serum aldolase determinations were elaborated according to the technique of Sibley and Lehninger.[15] The CRP was determined by the method of Tillet and Francis,[16] and the ESR by the method of Wintrobe and Landsberg.[17]

RESULTS

1. *Clinical.*—The normal range of plasma fibrinogen concentration varies from 210 to 390 mg. per cent, that of the SGO-transaminase from 10 to 40 units per milliliter, and the values of serum aldolase range from 5.5 to 8.5 units per milliliter. In accordance with previous experiences,[1] the fibrinogen concentration of patients with acute myocardial infarction reached the maximum values on the second and third days after onset of the symptoms, with peak levels ranging from 480 to 1,254 mg. per cent. The fibrinogen concentration, in uncomplicated cases, then declined to normal values by the end of the second, or during the third, week. The serum enzymes reached maximum concentration within 24 hours after onset. The peak values for the SGO-transaminase varied from 90 to 520 units per milliliter, and those of the serum aldolase ranged from 19 to 53 units per milliliter. The enzymes then rapidly declined and reached normal values on the fourth and fifth days of the disease. In 1 patient with a protracted

course and complicating pericarditis, the return of the fibrinogen level to normal was delayed until the end of the fourth week (Fig. 1).

In practically all patients with unequivocal coronary occlusion the CRP became significantly positive (2+ to 4+). However, this finding usually was unrelated to the clinical course, and in several instances this laboratory test was still as much as 4+ positive when the patients appeared clinically improved (Fig. 1). The ESR rose steeply shortly after onset of the disease, except for 7 patients who displayed hemoconcentration and shock on admission. In these

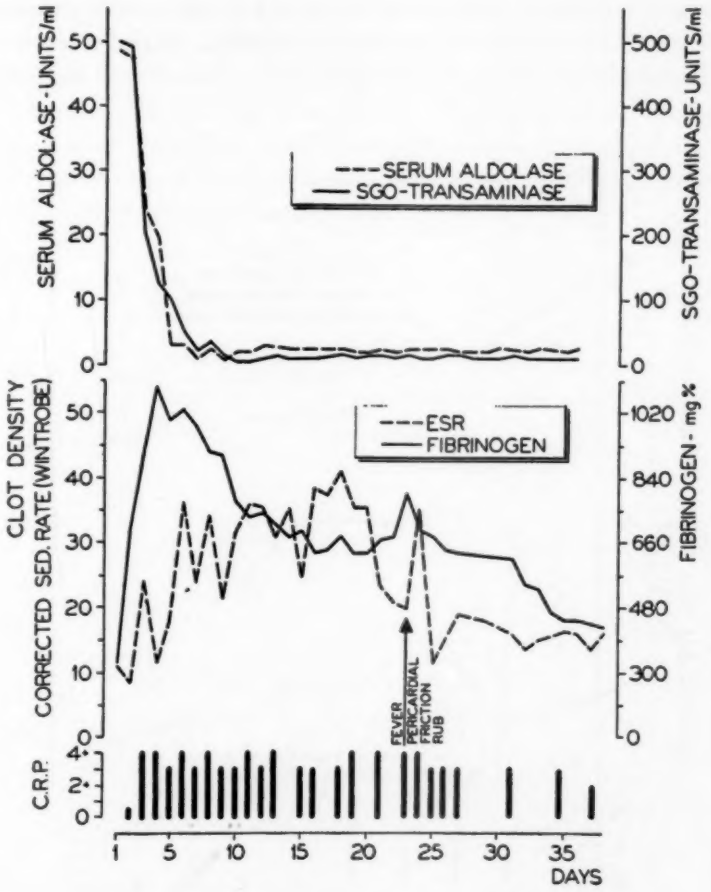

Fig. 1.—Serial determinations of fibrinogen concentration, SGO-transaminase, serum aldolase, ESR, and CRP in a 44-year-old man with massive posterior wall myocardial infarction.

instances the ESR remained within normal limits until the end of the second week, at which time it became significantly accelerated. In 14 patients whose course was entirely uneventful, the ESR was still considerably elevated upon discharge from the hospital, and up to 4 weeks after onset of the disease. In 2 cases the SGO-transaminase became but moderately elevated, and in another individual the serum aldolase remained within normal limits although the electrocardiographic readings indicated acute myocardial infarction and the

fibrinogen concentration, as well as the other respective serum enzymes, exhibited significant elevations.

In the group of patients whose diagnosis was established as either subendocardial necrosis or coronary insufficiency the enzymes either rose to slightly increased levels or remained within the upper limits of normal. Such changes are exemplified by graphs of an individual patient (Fig. 2). The SGO-transaminase never exceeded 65 or 70 units per milliliter, and the aldolase never rose above 13.5 units per milliliter. Similarly, the fibrinogen concentration remained slightly above or within normal limits. The CRP was negative, or occasionally changed to ± or 1+ positive results. The ESR was often considerably accelerated and in some instances remained so during the entire episode. Serial electrocardiographic changes in all these patients were not indicative of coronary occlusion.

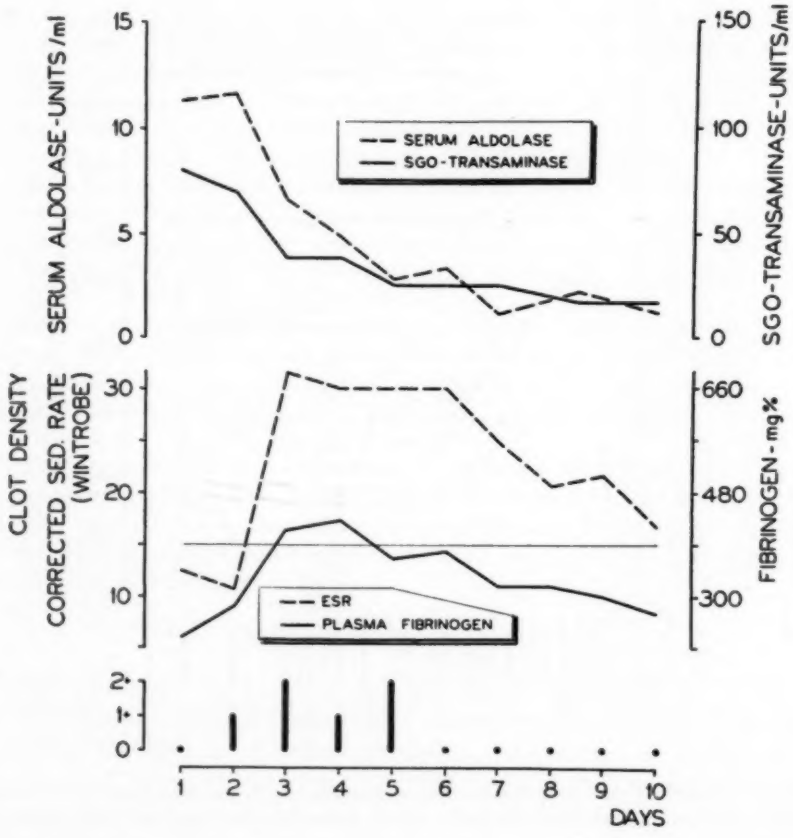

Fig. 2.—Serial determinations of fibrinogen concentration, SGO-transaminase, serum aldolase, ESR, and CRP in a 53-year-old man with subendocardial necrosis.

2. *Experimental.*—The preoperative serum aldolase level of all dogs of this series was in accord with the previously established normal for this species, namely, 15.71 units per milliliter (S.E. ±1.01).[16] The normal values of SGO-transaminase for these animals were 26.3 units per milliliter (S.E. ±1.0), and the normal fibrinogen concentration was 297 mg. per cent (S.E. ±6.06).

a. *High coronary ligation:* The mean maximum fibrinogen concentration of 595 mg. per cent was obtained on the fourth postoperative day and then declined to normal levels on the eighth postoperative day. The mean peak of the SGO-transaminase concentration reached 382 units per milliliter on the second day after coronary ligation and declined to normal levels 4 days later. The serum aldolase level rose to a mean maximum of 101.3 units per milliliter within 24 hours. Subsequently, the value declined until normal levels were obtained on the fifth postoperative day. The CRP values fluctuated from ± to 2+. A mean maximum CRP of 2+ was obtained on the fourth postoperative day and another mean peak of 2+ was observed on the eighth day after surgery. One of the animals had a negative CRP test throughout the entire observation period. The ESR fluctuated erratically. A mean maximum acceleration of 48 was noted on the fourth postoperative day. Subsequently, it declined to normal values on the seventh day, and reached another mean peak of 38 on the following day. Fig. 3 shows the serial laboratory data of a representative dog that had sustained a high coronary ligation.

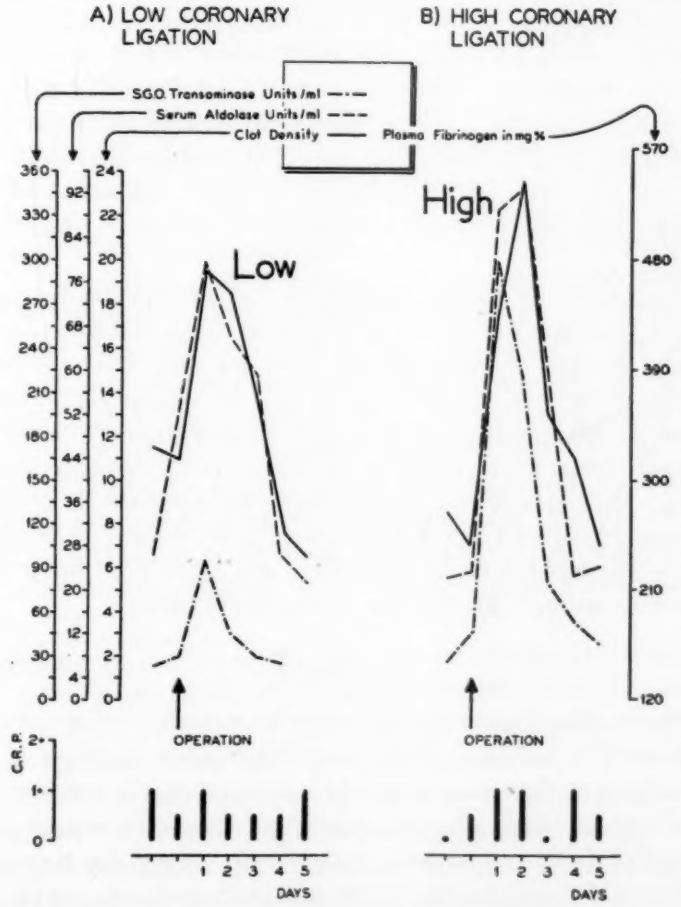

Fig. 3.—Serial determinations of fibrinogen concentration, SGO-transaminase, serum aldolase, ESR, and CRP in dogs subjected to low coronary ligation and high coronary ligation.

b. *Low coronary ligation:* The mean maximum fibrinogen concentration of 508 mg. per cent was obtained on the second postoperative day, and then declined to normal values on the next day. The SGO-transaminase rose suddenly and reached its mean peak level of 92 units per milliliter on the day following operation, from which peak it declined to normal levels within the next 3 to 4 days. The serum aldolase rose steeply to a mean peak of 59.2 units per milliliter within 24 hours after coronary ligation. It then decreased until it reached normal levels 3 to 4 days later. The mean postoperative values for the CRP fluctuated between ± and 2+. A maximum CRP of 2+ was noted in 1 animal on the eighth postoperative day. The ESR showed considerable fluctuations, with a mean maximum acceleration of 38 obtained 3 days after operation. From then on the ESR declined to 22 on the second day and rose again to a mean of 52 on the seventh day after coronary ligation. Fig. 3 demonstrates the serial determinations of these procedures in a dog who had sustained a low coronary ligation.

c. *Control studies:* A mean maximum fibrinogen level of 412 mg. per cent was recorded on the second postoperative day. This approximate level was sustained through the third day, regressed to normal on the fourth day, and remained normal thereafter. The SGO-transaminase rose to a mean level of 71 units per milliliter within 24 hours after sham-surgery, and then rapidly declined to normal on the third day. The serum aldolase followed a similar pattern of transient elevation, reaching a mean maximum of 40.5 units per milliliter, and then diminished to normal limits on the third postoperative day. The CRP fluctuated between ± and 1+ throughout the entire observation period. The ESR fluctuated erratically between a mean of 32 and 41, on the third and sixth days.

A gross inspection of hearts with high ligation revealed a wedge-shaped, soft, gray-white, mottled yellow area. In these dogs the lesion extended from the ligature at the base of the heart to the apex and involved practically the entire thickness of the left ventricle in an area of approximately 5.0 × 3.5 cm. In the specimens with low ligation a similar area of damaged tissue was seen to replace the heart muscle, but involving the correspondingly smaller zone of 1½ × 1½ cm. Microscopic studies disclosed the presence of granulation tissue in various stages of healing when the dogs were killed between the sixth and eighth days. On the ninth and the tenth days there was more prominent fibrosis noticeable. The control animals showed no myocardial change.

DISCUSSION

The ability to diagnose correctly acute myocardial infarction in cases with indefinite history or ambiguous electrocardiographic findings is obviously of decisive importance. The present study indicates that a battery of tests, consisting of the plasma fibrinogen concentration, the SGO-transaminase, and the serum aldolase, may be useful in supplementing electrocardiography and thus provide a more comprehensive profile of this clinical entity. This appears to be of particular value in those cases suspected of acute myocardial infarction and with atypical or masking electrocardiographic alterations.

None of the blood constituent elevations are specific expressions of acute myocardial necrosis. The enzymes are present in various organs, including heart muscle and liver.[18,19] Necrosis of these tissues, as in acute myocardial infarction or hepatic disease, leads to their release into the peripheral circulation. Thus, acute coronary occlusion with subsequent myocardial infarction leads to a short-lasting but significant elevation of SGO-transaminase and serum aldolase of 4 to 5 days' duration, with the peak reached within 1 to 2 days after onset of the symptoms. The hyperfibrinogenemia observed in acute myocardial infarction is also a nonspecific reaction to traumatized tissue or to an inflammatory process.[2] Its elevation, however, rather expresses the phase of repair or healing. The maximum hyperfibrinogenemia following acute myocardial infarction occurs, therefore, later than the peak of serum enzyme activity, i.e., on the second to third day after coronary occlusion.[1,2] This is followed by a gradual decline until normal values are reached at the end of the second, or during the third, week.

The accumulated evidence indicates that a marked elevation of the aforementioned enzymes is highly suggestive of myocardial necrosis, provided other tissue necrosis or liver disease can be excluded. A marked increment of fibrinogen occurs also in a similar condition, except for hepatic disease, where the fibrinogen level tends to be low normal or subnormal, the liver being the principal source of fibrinogen production.

In animal experiments a semiquantitative correlation exists between the extent of infarction and the peak of enzyme[6,20,21] and fibrinogen levels.[22] The mean peak of all 3 blood constituents is significantly higher, in comparison, in the dogs with high coronary ligation than in those who were subjected to low ligation. Similar to the experiences in patients with acute myocardial infarction, and in accord with previous observations in dogs with experimental transmural infarction, both enzymes reached maximum concentration on the second postoperative day and returned to normal values 4 days later. On the other hand, the maximum fibrinogen concentration was attained on the third day after coronary ligation, while the return to normal occurred between the fifth and seventh postoperative days. The more moderate and relatively short-lasting hyperfibrinogenemia which was observed in the dog, as compared with the results obtained in man, was interpreted previously as being inherent to this species.[22] The relatively insignificant, short-lived postoperative rise of these values in the control experiments is attributed to the tissue injury caused by the surgical manipulation.

A correspondence between the size of experimental infarction and the degree of elevation of the serum enzymes and plasma fibrinogen is evident from the presently reported data. A similar correlation in human beings cannot be established as readily. However, there appears to be a distinct relationship between the severity of the clinical status and the incremented serum enzymes and fibrinogen levels. Thus, in a previous study of a series of 75 patients with acute myocardial infarction, the authors observed a fourfold mortality rate increase in a subgroup of cases with maximal fibrinogen concentration exceeding 800 mg. per cent.[2] There is a strong indication that very high enzyme peak levels similarly constitute an ominous prognostic sign.[5,6]

From a clinical viewpoint it seems, therefore, that neither the enzymes nor the fibrinogen concentration alone adequately reflect the totality of the myocardial injury. However, when applied conjointly and serially these tests are useful tools to supplement the electrocardiographic changes. The enzymes indicate not only the severity of the disease, but, due to their rapid increase in the serum, also frequently suggest the presence of acute myocardial infarction prior to the occurrence of diagnostic electrocardiographic changes. However, since they return to normal levels on about the fifth day of the disease, these tests give no information as to the further course of the illness unless an extension of the myocardial infarction following the initial insult occurs. On the other hand, the fibrinogen concentration, although its peak is not attained prior to the second to third day, reflects more accurately the recovery stage. In those patients whose course of disease is protracted, the return of the fibrinogen concentration frequently is delayed until the end of the fourth week, or even longer. Moreover, a transient rise of the fibrinogen concentration during the stage of convalescence mirrors not only an extension of the myocardial necrosis, but also such complications as intercurrent pericarditis, heart failure with pulmonary edema or pulmonary embolization, which apparently are not indicated by any recurrent increase of the serum enzyme levels.

Recently, false negative results obtained with the SGO-transaminase have been reported in patients with unequivocal myocardial infarction,[23,24] an observation which has been confirmed by this study. Two of our patients had an insignificant rise of the SGO-transaminase in the presence of an elevated serum aldolase and fibrinogen concentration. On the other hand, in 1 patient, also with proved myocardial infarction, the serum aldolase failed to rise, while significant increases of the SGO-transaminase and fibrinogen concentration confirmed electrocardiographic changes. Thus far in our experience, the fibrinogen level never failed to rise in patients with unequivocal myocardial infarction. Misleading negative results obtained with 1 enzyme determination can, therefore, be obviated by simultaneous studies of the SGO-transaminase, the serum aldolase, as well as the fibrinogen concentration. Moreover, since all 3 tests display at best a moderate rise in patients with coronary insufficiency or subendocardial necrosis,[1,5,6] this battery of procedures in conjunction with serial electrocardiographic studies can be utilized to advantage for the establishment of the correct diagnosis of such conditions. It appears that a moderate rise of the SGO-transaminase to 60 or 70 units per milliliter in the presence of normal serum aldolase levels and plasma fibrinogen concentration indicates the existence of a subendocardial necrosis.

The aforementioned laboratory procedures can be carried out easily in any well-equipped laboratory. The methods for the enzyme determinations require no special technical skill and all necessary reagents are commercially available. Care has to be taken to avoid hemolysis of the serum which may alter the data. The fibrinogen determination carried out by the clot density method as elaborated by the authors[13] can be completed within 5 minutes; its additional advantage is that the test simultaneously yields the prothrombin time. This is of considerable importance in those patients under anticoagulant therapy with hypoprothrom-

binemic agents, such as Dicumarol, Hedulin, or Tromexan. None of these anticoagulants affect the fibrinogen concentration.[2]

The aforementioned 3 laboratory procedures were compared with the CRP and the ESR since these tests are used in the evaluation of patients with acute myocardial infarction. In the experimental animals the acceleration of the ESR was rather erratic and without correlation to the extent of the myocardial infarction or to the time of healing. Similarly, in patients with acute coronary occlusion, the ESR frequently failed to show a close correlation with the clinical conditions. Thus, the ESR on many occasions has been observed to remain accelerated long after apparent recovery.[1,13] Moreover, the ESR frequently failed to indicate the severity of the disease process, particularly in subjects with initial shock and hemoconcentration.[2,3] It was demonstrated in vivo and by in vitro experiments that a high hematocrit reading has a definitive retarding effect on the ESR which then becomes accelerated only after the hematocrit declines to normal values. Furthermore, as previously reported and confirmed in this study, the ESR may be accelerated significantly in patients with coronary insufficiency,[1,2] thereby confusing the diagnosis.

The great simplicity of the method for measuring the CRP has led also to its application in patients with acute coronary occlusion. However, the procedure has been reported by some to give variable results.[25] In patients with acute myocardial infarction the test usually becomes positive within 24 to 48 hours[26,27]; however, it does not reflect the severity nor does it correlate with the duration of the disease.[25] While in some instances it becomes rapidly negative, in other patients the procedure remains positive for many days or weeks after apparent healing of the infarct has occurred.

SUMMARY

A battery of tests consisting of serial determinations of plasma fibrinogen, SGO-transaminase, serum aldolase, the C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) was applied to patients with acute myocardial infarction, subendocardial necrosis, and coronary insufficiency, as well as to a group of dogs with ligation of the left anterior coronary artery at various levels.

In the patients with acute myocardial infarction the enzymes reached their maximum concentration within 1 to 2 days after onset of the symptoms, and returned to normal 3 to 4 days later. The peak of fibrinogen concentration appeared on the second or third day following coronary occlusion, and returned to normal levels at the end of the second or during the third week. The maximum level of all 3 blood constituents reflected the gravity of the disease. During the stage of convalescence, recurrent elevations of both the enzymes as well as the fibrinogen concentration mirrored an extension of the myocardial infarction. The fibrinogen level, moreover, reflected a protracted clinical course and indicated such complications as intercurrent pericarditis, heart failure with pulmonary edema or pulmonary embolization. On the other hand, in patients with coronary insufficiency or subendocardial necrosis, all 3 blood constituents remained within normal levels or occasionally showed very moderate elevations. It is concluded that neither the enzymes nor the fibrinogen concentration alone adequately

reflect the totality of the myocardial injury, but when applied conjointly and serially, they are useful tools to supplement the electrocardiographic findings.

The ESR and the CRP usually attain abnormal values in acute coronary occlusion. However, they neither reflect the severity nor the duration of the disease. Moreover, the ESR frequently is considerably accelerated in patients with coronary insufficiency.

In dogs with experimentally produced myocardial infarction the enzymes reached their peak levels within 24 hours, and the fibrinogen within 2 days after operation. A semiquantitative relationship between the extent of myocardial infarction and the maximum concentration of these blood constituents exists.

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STUDIES OF PULMONARY HYPERTENSION. VIII

Effects of Acetyl Strophanthidin on Pulmonary Circulation in Patients With Cardiac Failure and Mitral Stenosis

Paul N. Yu, M.D., Robert E. Nye, Jr., M.D., Frank W. Lovejoy, Jr., M.D.
José de J. Macias, M.D.,* Bernard F. Schreiner, M.D.,**
and James J. Lux, M.D.,***

Rochester, N. Y.

With Technical Assistance of Ruth Knight and Ann Podgers

THE hemodynamic effects of intravenous digitalis-like preparations have been studied in normal subjects and in patients with various cardiopulmonary diseases by many investigators.[1-15] It is agreed generally that digitalis exerts its primary action on the myocardium. Following acute digitalization there may be a reduction in the cardiac output and no change in the pulmonary artery and right ventricular end-diastolic pressures in normal subjects and in patients without cardiac failure. In patients with cardiac failure, digitalis has been found to reduce the end-diastolic pressure of the right ventricle and probably the residual blood volume in the heart, and to increase the cardiac output and left ventricular efficiency. In patients with predominant left ventricular failure there is usually a decrease in the pulmonary artery pressure. In those with predominant right ventricular failure and restricted pulmonary vascular bed there may be a transient rise in the pulmonary artery pressure despite a reduction in the right ventricular end-diastolic pressure.

The recent studies of acetyl strophanthidin by Lown and Levine[16] indicate that the drug produces its earliest effect upon the electrocardiogram within 1 to 5 minutes, and reaches its peak action in 12 minutes; and that its effect may persist for about 1 to 2 hours. The onset and dissipation of the effect of acetyl strophanthidin are more rapid than of any other presently known digitalis-like preparation.[16,17] The drug has been found to be useful in ascertaining the "digitalis status of cardiac patients."[16] To our knowledge, no studies of the effect of acetyl strophanthidin on pulmonary circulatory dynamics in patients have been reported. It is the purpose of this paper to report hemodynamic effects of the drug in patients with combined ventricular failure, left ventricular failure, and pre-

From the Chest Laboratory of the Department of Medicine, the University of Rochester School of Medicine and Dentistry, and the Medical Clinics of Strong Memorial and Rochester Municipal Hospitals.

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*Kellogg Foundation Fellow, 1955-57.

**National Heart Institute Trainee, 1954-55.

***National Heart Institute Trainee, 1955-56.

dominant mitral stenosis. It is, also, an attempt to differentiate the response in patients with predominant mitral stenosis from that of those in left ventricular failure.

CLINICAL MATERIAL AND METHODS

Three groups of patients were studied: (1) 3 patients with combined ventricular failure, (2) 4 patients with predominant left ventricular failure, and (3) 4 patients with predominant mitral stenosis.

No patient had received a digitalis preparation within 4 weeks prior to the study. The criteria used for diagnosis were those adopted by the New York Heart Association. The classification of the functional capacity represents the clinical status at the time of study.

The clinical diagnosis of combined ventricular failure was made by the presence of peripheral edema, increased venous pressure, hepatomegaly, and pulmonary congestion in each case. Hemodynamically, there was elevation of pulmonary artery, pulmonary "capillary," right ventricular end-diastolic and right atrial pressures. None of these patients had evidence of valvular disease or constrictive pericarditis. One of the 3 patients (A.M.) had hypertensive cardiovascular disease, but in the remaining 2 patients (S. N. and H. Mc.) the etiological factor was uncertain.

Patients were classified as having predominant left ventricular failure when signs of pulmonary congestion were elicited, the venous pressure was normal, and there was no peripheral edema. Two patients with mitral valve disease were included in this group when a significant reduction in pulmonary artery and pulmonary "capillary" pressures followed administration of acetyl strophanthidin.

One patient (T. M.) had predominant aortic stenosis of rheumatic origin. The physiologic studies were made 3 months prior to aortic valvulotomy which was performed under hypothermia. The left ventricular end-diastolic pressure was 25 mm. Hg, and there was a systolic pressure gradient of 50 mm. Hg across the aortic valve measured at the operating table. The patient died of ventricular fibrillation after the fracture of the aortic valve and the post-mortem examination showed no evidence of mitral valve disease. One patient (G. M.) had predominant mitral insufficiency of rheumatic origin with clinical signs of pulmonary congestion. The third patient (C. D.) had rheumatic heart disease with mitral stenosis and insufficiency and atrial fibrillation. His heart was markedly enlarged and there were clinical signs of pulmonary congestion at the time of study. The fourth patient (C. M.) also had mitral stenosis and insufficiency of rheumatic origin. He had been on digitalis therapy for several years. Eight months following mitral valvuloplasty he felt so well that he discontinued digitalis without his physician's advice. Three weeks later he was seen because of an attack of acute breathlessness following a half-mile walk. On examination there were physical signs of acute pulmonary edema which disappeared after a short period of rest. A posteroanterior chest film compared with the preoperative film showed some reduction in over-all size of the heart, but the contour was more boot-shaped than before. It was thought that he might have myocardial insufficiency associated with mitral valvular disease. Salt restriction was enforced. Digitalis was withheld pending study of the acute effect of acetyl strophanthidin, which was made about 9 months after mitral valvuloplasty.

Patients were classified as having predominant mitral stenosis when the administration of acetyl strophanthidin failed to produce significant changes in the pulmonary artery and pulmonary "capillary" pressures. This group contained 4 patients. Following the studies, mitral valvuloplasty was performed on 2 patients. Tight mitral stenosis was present in one (L. T.), and moderate mitral stenosis with slight mitral insufficiency in the other (R. P.). However, direct pressure tracings obtained from the left ventricle in patient R. P. before and after operation showed no evidence of left ventricular failure. Mitral valve surgery was not recommended for the remaining 2 patients because their disease was mild.

The patients were studied in the postabsorptive state. In most cases Noludar* 150 mg. was given as premedication. In all patients a single lumen #7 or #8 long Cournand catheter was used. Pressures were recorded by means of a Statham pressure transducer connected to an amplifier in a Sanborn Poly-Viso Cardiette. A control electrocardiogram was obtained in each patient before the introduction of the catheter.

*Courtesy of Hoffmann-LaRoche, Inc., Nutley, N. J.

Immediately after the determination of the cardiac output by the direct Fick principle, brachial and pulmonary artery pressures were recorded. Following this, pulmonary "capillary" pressure (pulmonary artery wedge pressure) was obtained in all but 1 patient. Acetyl strophanthidin* diluted with physiologic saline was injected through the catheter into the pulmonary artery at a rate of approximately 0.1 mg. per minute. Electrocardiographic tracings were recorded every minute. The injection was discontinued immediately whenever there was a prolongation of the P-R interval, significant slowing of the ventricular rate, or appearance of ventricular premature contractions. No patient complained of nausea or vomiting during the injection. In most cases 1.0 to 1.2 Gm. of acetyl strophanthidin was used. In two cases (G. N. and C. D.) 0.75 mg. was injected, and in one case (S. N.) 1.5 mg. No untoward effect was noticed in any patient.

TABLE I. DATA OF TWO SUCCESSIVE DETERMINATIONS DURING CARDIAC CATHETERIZATION IN NINE PATIENTS STUDIED FOR DIAGNOSTIC PURPOSES

CASES	PA_m		PC_m		PA_m-PC_m		TPR		PVR		MVR	
	A	B	A	B	A	B	A	B	A	B	A	B
R. K.	11	10	5	3	6	7	80	90	50	60	30	30
G. S.	13	13	9	8	4	5	160	160	60	50	100	110
C. T.	16	14	12	11	4	3	370	330	90	70	280	260
M. C.	27	26	10	10	17	16	670	640	420	400	250	240
M. B.	31	30	21	21	10	9	660	610	220	180	440	430
D. K.	32	28	20	19	12	9	480	500	180	200	300	300
E. O.	32	37	20	25	12	12	1890	2120	710	690	1180	1430
M. S.	37	29	24	20	13	9	550	480	200	150	350	330
E. S.	47	45	25	22	22	23	1060	970	500	450	560	520
Mean	27	26	16	15	11	11	658	656	270	250	388	406
Standard Error of Mean	±4	±4	±2	±2	±2	±2	±182	±203	±79	±73	±112	±137

Pressures in mm. Hg.
PA_m = pulmonary artery mean pressure.
PC_m = pulmonary "capillary" mean pressure.
PA_m-PC_m = pulmonary artery to pulmonary "capillary" mean pressure gradient.
Resistances in dynes-sec.-cm.$^{-5}$
TPR = total pulmonary resistance.
PVR = pulmonary vascular resistance.
MVR = "mitral valve resistance."
A = first determination; B = second determination.

Pulmonary artery and brachial artery pressure tracings were obtained at frequent intervals during the acetyl strophanthidin injection. One or two subsequent determinations of cardiac output were made between 21 and 74 minutes after the start of the injection of the durg. Following each determination, brachial and pulmonary artery pressures were again recorded and in all but 2 patients pulmonary "capillary" pressure was measured. Towards the end of the procedure right ventricular and right atrial pressures were recorded.

The heart rates were computed from the electrocardiogram taken immediately after cardiac output determination. The methods of analyzing pressure tracings and blood gases, and calculating the systemic and pulmonary resistances have been previously described.[18] Pulmonary vascular resistance is the resistance encountered between pulmonary artery and pulmonary vein, employing pulmonary "capillary" pressure as an index of pulmonary venous pressure. Total pulmonary

*Courtesy of Eli Lilly and Company, Indianapolis, Ind.

TABLE II. CLINICAL DATA

CASE	AGE	SEX	B.S.A. M.^{2}	FUNCTIONAL CLASSIFICATION	EXERTIONAL DYSPNEA	SYMPTOMS AND SIGNS		VENOUS DISTENTION	HEPATOMEGALY	PERIPHERAL EDEMA	B.P.	RHYTHM	CARDIAC ENLARGEMENT (ROENTGENOGRAM)	REMARKS
						P.N.D.	PULMONARY CONGESTION							
A.M.	43	M	1.72	IV	+	+	+	+	+	+	150/115	S.R.	L.V., R.V.	
S.N.	36	M	2.08	IV	+	0	+	+	+	+	104/74	S.R.	L.V., R.V.	Gallop
H.Mc.	47	F	1.47	IV	+	0	+	+	+	+	124/80	S.R.	L.V., R.V.	
T.M.	30	F	1.76	III	+	+	+	0	0	0	102/76	S.R.	L.V.	Angina
G.M.	34	F	1.64	III	+	+	+	0	0	0	102/70	S.R.	L.V.	
C.D.	41	M	1.70	III	+	+	+	0	+	0	130/100	A.F.	L.V., R.V., L.A.	Hemoptysis
C.M.	32	M	1.75	III	+	+	+	0	0	0	120/70	S.R.	L.V., R.V., L.A.	
M.R.	47	F	1.46	II	+	+	0	0	0	0	120/78	S.R.	R.V., L.A.	
R.C.	32	F	2.01	II	+	0	0	0	0	0	120/70	S.R.	R.V., L.A.	
L.T.	44	F	1.74	III	+	+	0	0	0	0	112/60	S.R.	R.V., L.A.	
R.P.	40	F	1.65	III	+	0	0	0	0	0	126/80	S.R.	R.V., L.V., L.A.	

B.S.A. (M.^{2}) = Body surface area in square meter.
P.N.D. = Paroxysmal nocturnal dyspnea.
S.R. = Sinus rhythm.
A.F. = Atrial fibrillation.
L.V. = Left ventricle.
R.V. = Right ventricle.
L.A. = Left atrium.
B.P. = Blood pressure.

resistance includes also the resistance to filling offered by the left ventricle and mitral valve. The difference between total pulmonary resistance and pulmonary vascular resistance has been termed "mitral valve resistance."[19] The arbitrary zero point of all pressures with the patient recumbent was 6.5 cm. posterior to the angle of Louis. Respiratory exchange ratio (R. Q.) was determined by duplicate analysis of samples of mixed expired air taken during the minute when oxygen consumption was measured, using the Scholander 0.5 gas analyzer.

The ranges of variation in oxygen consumption, A-V oxygen difference, cardiac index, heart rate, stroke index, pulmonary artery mean pressure and the total pulmonary resistance in 2 successive control determinations in 36 patients were presented in detail in a previous paper.[18] It was shown that any changes beyond the following ranges were considered significant:

Oxygen consumption + 13% or −10%
Cardiac index + 13% or −10%
Stroke index + 7 c.c. or −5 c.c./M.²/beat
Pulmonary artery pressure + 5 mm. Hg or −8 mm. Hg
Total pulmonary resistance + 20% or −30%

The variation of oxygen consumption in the present study from period A (control) to period B (after acetyl strophanthidin) was less than + 13 per cent or −10 per cent in all cases except one (A. M.). In this patient the oxygen consumption in period A was 170 c.c./M.²/min. and in period B, 149 c.c./M.²/min., a decrease of 17 per cent. The high oxygen consumption in period A was due most likely to anxiety. However, the experiment is included because the increase in cardiac output in period B would be even more significant had the control cardiac output been lower.

In the previous paper,[18] because of too few cases, no data on the range of variation in pulmonary "capillary" pressure and pulmonary vascular resistance were included. Since then, studies have been made on a series of 9 patients with 2 successive control determinations of blood flow and pressures. Pulmonary artery and pulmonary "capillary" pressures were measured immediately following the determination of each cardiac output; the average time between the two determinations in these 9 cases was 20 minutes. None of these patients in between the control determinations was subjected to any special studies or procedures.

As shown in Table I, the difference between 2 successive measurements of the pulmonary "capillary" pressure was 5 mm. Hg or less. The range of variation of the pulmonary vascular resistance from the first to the second determination was ± 25 per cent and that of the "mitral valve resistance"[19] was ± 20 per cent. It was our observation that whenever there was an increase or decrease in the pulmonary artery pressure, the pulmonary "capillary" pressure almost always changed in the same direction. Therefore, the pulmonary artery to pulmonary "capillary" pressure gradient remained fairly constant, changing by 4 mm. Hg or less.

RESULTS

The clinical data of the 11 patients are summarized in Table II. The hemodynamic effects of intravenous acetyl strophanthidin are presented in Table III.

Group 1: Combined Ventricular Failure.—Following the intravenous injection of acetyl strophanthidin, the most significant change in all 3 patients was an increase in cardiac index ranging from 42 to 57 per cent. The increase in the cardiac index was manifested by a marked reduction of A-V O_2 difference. In all there was a significant increase in the stroke index.

The change in the pulmonary artery pressure was insignificant in patients A. M. and S. N. A significant decrease in the pulmonary artery pressure was observed in patient H. Mc. 40 minutes after the start of injection. However, 22 minutes later the pulmonary artery pressure in this patient rose and approached the control level.

TABLE III. HEMODYNAMIC EFFECTS OF ACETYL STROPHANTHIDIN

CASE	PERIODS OF STUDY	BLOOD FLOW				BLOOD PRESSURES (MM. Hg)					RESISTANCES (DYNES-SEC.-CM.$^{-5}$)			R.Q.
		A-V O_2 DIFFERENCE	C.I.	H.R.	S.I.	B.A. OR F.A.	PA	"PC"	PA-"PC"	RV	TSR	TPR	PVR	
Group 1—Combined Ventricular Failure														
A.M.	A	99.0	1.70	103	17	130	56	30	26		3540	1520	710	0.78
	B (25)	58.9	2.42	97	25	141	51	28	23	66/9	2660	970	440	0.74
S.N.	A	42.1	3.37	120	28	—	38	32	6		—	430	70	—
	B (26)	28.0	4.97	116	43	94	38	—	—		730	290	—	—
	(43)	24.7	5.30	117	45	—	—	—	—	55/13	—	—	—	—
H.Mc.	A	81.5	1.48	100	15	116	58	19	39		4250	1830	1140	—
	B (40)	66.5	2.11	91	23	114	47	—	—		3390	1400	—	0.95
	(62)	58.2	2.28	95	24	105	52	20	32	79/25	2500	1240	840	0.87
Group 2—Predominant Left Ventricular Failure														
T.M.	A	54.7	2.85	97	29	73	41	37	4		1160	650	60	0.90
	B (74)	48.0	3.12	93	34	83	35	28	7	46/6	1190	510	130	0.75
G.M.	A	48.4	2.56	100	26	75	36	22	14		1430	690	270	—
	B (29)	49.3	2.53	81	29	77	27	—	—		1610	510	—	—
	(45)	46.2	2.66	79	34	56	22	10	12	29/3	1030	400	210	—
C.D.	A	89.6	1.67	122	14	90	60	—	—		2490	1660	—	0.77
	B (21)	65.0	1.85	74	25	85	50	—	—		2130	1250	—	0.81
	(43)	70.6	1.97	74	27	81	47	—	—	62/4	1900	1100	—	0.75
C.M.	A	72.0	1.51	80	19	82	59	25	34		2480	1790	1060	0.88
	B (24)	67.0	1.66	65	25	76	48	19	29	92/2	2110	1330	800	0.84

Group 3—Predominant Mitral Stenosis

M.R.	A	37.7	3.82	80	48	88	29	16	13		1260	420	190	—
	B (24)	37.7	3.53	79	45	86	21	13	8	33/3	1340	330	120	—
R.C.	A	37.1	2.61	70	37	87	28	18	10		1380	430	150	—
	B (22)	35.9	2.56	58	44	85	22	19	3	36/6	1320	340	50	—
L.T.	A	47.3	2.39	63	38	88	41	21	20		1670	780	400	0.82
	B (21)	50.8	2.30	59	39	89	43	20	23	70/5	1756	850	450	0.79
R.P.	A	60.7	2.10	103	21	107	35	21	14		2460	800	320	0.82
	B (25)	49.9	2.50	80	32	100	27	18	9		1900	510	170	0.92
	(54)	54.1	2.40	100	24	91	29	17	12	37/6	1810	580	240	0.76

A = Control period.
B = Period after acetyl strophanthidin injection; the figures in parentheses indicate minutes after the start of injection.
A-V O_2 difference = Arteriovenous blood oxygen difference (c.c./L.).
C.I. = Cardiac index (L./M.^{2}/min.).
H.R. = Heart rate (beats/min.).
S.I. = Stroke index (c.c./M.^{2}/beat).
B.A. or F.A. = Brachial or femoral artery mean pressure.
PA = Pulmonary artery mean pressure.
"PC" = Pulmonary "capillary" mean pressure.
PA-"PC" = Pulmonary artery to pulmonary "capillary" mean pressure gradient.
RV = Right ventricular systolic and end-diastolic pressures.
TSR = Total peripheral resistance.
TPR = Total pulmonary resistance.
PVR = Pulmonary vascular resistance.
R.Q. = Respiratory exchange ratio.

There was no significant change in the pulmonary "capillary" pressure in 2 patients (A. M. and H. Mc.) in whom it was recorded.

The change in systemic artery pressure in 2 cases was variable, although in each case there was a reduction in the total peripheral resistance.

The total pulmonary resistance was significantly reduced in all 3 cases, as was the pulmonary vascular resistance in 2 patients in whom it was measured. The right ventricular end-diastolic pressure, obtained at the end of the procedure remained elevated in each case.

Group 2: Predominant Left Ventricular Failure.—In contrast to the patients in Group 1, following acetyl strophanthidin administration, the most constant and significant change in this group of patients was the striking and consistent decrease in the pulmonary artery and pulmonary "capillary" pressures (see Table III). In some instances the reductions in pressure were greater than appear in the table. For example, in patient C. D. the pulmonary artery pressure fell to 38 mm. Hg at the thirty-fifth minute, and in patient C. M. the pulmonary "capillary" pressure was 16 mm. Hg at the twenty-ninth minute.

After acetyl strophanthidin 3 of the 4 patients (G. M., T. M., and C. M.) in this group showed an insignificant rise in cardiac index. In patient C. D. the cardiac index rose 18 per cent which, although beyond the range of spontaneous variation in our control series, is certainly less impressive than in patients with combined ventricular failure. In patients G. M. and C. D. there was a significant increase in the stroke index.

The systemic artery pressure declined in 3 of 4 patients (G. M., C. D., and C. M.), whereas in patient T. M. it rose slightly following the acetyl strophanthidin administration.

In all 4 patients the right ventricular end-diastolic pressure was normal, recorded about an hour or more after the start of injection of the drug.

The total peripheral resistance was reduced in 3 patients and remained unchanged in patient T. M.

The total pulmonary resistance decreased in all 4 patients, being significant in only 2 patients, G. M. and C. D.

The change in the pulmonary vascular resistance was variable, decreased insignificantly in 2 and increased in 1.

Group 3: Predominant Mitral Stenosis.—After acetyl strophanthidin there was no change in the cardiac index in 3 of 4 patients (M. R., R. C., and L. T.) and a slight increase of 19 per cent in patient R. P. The change in stroke index in the first 3 patients was insignificant. Although in patient R. P. the stroke index increased significantly at the twenty-fifth minute from the start of injection of acetyl strophanthidin, it returned almost to the control level 29 minutes later.

Following acetyl strophanthidin none of the 4 patients showed significant change in the pulmonary artery and pulmonary "capillary" pressures. The total pulmonary resistance tended to fall but the reduction was significant only in 1 patient (R. P.) in whom there was also a decrease in "mitral valve resistance." Pulmonary vascular resistance significantly decreased in 3 of 4 patients (M. R., R. C., and R. P.) and showed no change in the fourth (L. T.). The systemic

pressure and peripheral resistance remained unchanged in patients M. R., R. C., and L. T., and slightly decreased in patient R. P.

DISCUSSION

In patients with predominant left ventricular failure acetyl strophanthidin decreased the pulmonary artery and pulmonary "capillary" pressures with or without raising the stroke index and the cardiac index. In the absence of mitral valvular obstruction a reduction of the pulmonary "capillary" pressure indicates a decrease in the left ventricular end-diastolic pressure. This suggests that the myocardial function of these patients improved with more adequate emptying of the left ventricle, because the same cardiac output was now maintained with a lower filling pressure.

In patients with combined ventricular failure, on the other hand, cardiac index and stroke index rose without significant change in the pulmonary artery or pulmonary "capillary" pressure. One may regard this as the resultant of 2 effects of acetyl strophanthidin on the failing ventricles: first, the tendency to raise the pulmonary artery pressure in predominant right ventricular failure, as demonstrated by Ferrer and associates[8] in cases of cor pulmonale (in their cases attributed to increased right ventricular output into a restricted vascular bed); and second, the tendency to lower the pulmonary artery and the pulmonary "capillary" pressures in cases of predominant left ventricular failure. The combined effect might well be to increase flow without change in pressures.

Following the administration of acetyl strophanthidin, there was a significant reduction in the total pulmonary resistance in all 3 patients with combined ventricular failure and in 2 patients (G. M. and C. D.) with predominant left ventricular failure. The reduction was observed only in those patients who showed a significant increase in the stroke index after acetyl strophanthidin. The effect of acetyl strophanthidin upon the total pulmonary resistance (TPR) is best considered in terms of its 2 components: the pulmonary vascular resistance (PVR) residing mainly in the pulmonary arterioles and capillaries, and the balance (TPR-PVR) offered by the mitral valve and the left ventricular contents during diastole, which has been termed the "mitral valve resistance."[19] The latter declined by from 27 to 55 per cent of the control value in all patients thought to have left ventricular failure, either alone or in combination with right ventricular failure, in whom the measurement was obtained. This was due probably to improvement of the left ventricular function either in increased flow or in decreased left ventricular end-diastolic pressure, or in a combination of both.

The response of patients with predominant mitral stenosis without cardiac decompensation was different in some respects from those with cardiac failure. Following acetyl strophanthidin, there was no appreciable or consistent change of either stroke index or cardiac index. This is in agreement with the results obtained by Harvey and her associates[11] and Bloomfield and his co-workers.[12] No significant change occurred in the pulmonary "capillary" and pulmonary artery pressures. A significant fall in the total pulmonary resistance occurred only in one patient (R. P.), in whom the drug induced a barely significant increase in cardiac index and an insignificant fall in pulmonary artery and pulmonary "capil-

lary" pressures. In the same patient there was also a distinct fall in the "mitral valve resistance" (i.e., more than 20 per cent of the control value). The reason for this was not apparent, although there is a possibility that this patient might have had latent left ventricular failure at the time of study.

The importance of differentiating the mechanical and myocardial factors in patients with mitral stenosis has been emphasized by Harvey and her associates.[15] In general, in patients with predominant mitral valvular obstruction, pulmonary hypertension is more severe, cardiac output is higher, and the heart size is smaller than in those with predominant myocardial insufficiency. In many patients with mitral stenosis, both mechanical obstruction and myocardial insufficiency may be present. Hence, it is difficult to separate the two components in a given patient. A satisfactory way of demonstrating the presence and the degree of myocardial insufficiency in these patients is much needed. The results of the present study may offer such a means of differentiation. As the present series of cases is too small to draw any definite conclusion, a preliminary statement may be made as follows. Following the administration of acetyl strophanthidin in patients with predominant myocardial insufficiency, the stroke index may increase and the pulmonary "capillary" pressure and "mitral valve resistance" decrease, whereas in patients with predominant mitral valvular obstruction no significant change occurs in any of these determinants. The pulmonary artery pressure may decrease significantly in patients with predominant left ventricular failure but not in those with predominant mitral stenosis.

SUMMARY AND CONCLUSIONS

The acute hemodynamic effects of acetyl strophanthidin have been studied in 11 patients who were not digitalized prior to the study.

In 3 patients with combined left and right ventricular failure, cardiac index and stroke index rose, while pulmonary vascular resistance and "mitral valve resistance" fell. The pulmonary artery and pulmonary "capillary" pressures did not change.

Four patients with predominant left ventricular failure had significant decreases in pulmonary artery and pulmonary "capillary" pressures and in "mitral valve resistance." Stroke index increased in 2 patients, but the changes in cardiac index and pulmonary vascular resistance were inconsistent.

Three of 4 patients with predominant mitral stenosis showed neither increase in output nor decrease in pulmonary vascular pressures, nor changes in "mitral valve resistance." The fourth patient with predominant mitral stenosis, who behaved atypically, probably had some latent left ventricular failure. Three of these patients had reductions in the pulmonary vascular resistance which is unexplained.

It is believed that the administration of acetyl strophanthidin under careful electrocardiographic control to patients not already digitalized is a safe and informative procedure. Of particular interest is the assessment of left ventricular failure in patients with mitral stenosis by the behavior of "mitral valve resistance," which includes the resistance offered by the left ventricle to filling, and which may provide a more sensitive index of associated left ventricular failure than pressure or flow changes considered independently.

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VENTRICULAR GALLOP IN MITRAL STENOSIS. ITS MECHANISM AND SIGNIFICANCE

STEPHEN CONTRO, M.D.*

CHICAGO, ILL.

THE auscultatory characteristics of mitral stenosis, although well defined many years ago, still remain poorly explained. Duroziez[1] in 1862, first gave a complete description of these acoustic findings and embraced them into the classic formula "fffout-ta-ta-rou." The studies of other clinicians confirmed Duroziez's description. Controversies began to arise in an attempt to explain these acoustics on the basis of the hemodynamics of this valvular defect and to correlate them more adequately with the mechanical events of the cardiac cycle.

Among the many debated questions, there has been particular interest in the mechanism of the triple rhythm encountered in this disease, illustrated by the second "ta" of Duroziez. Duroziez believed that this extra sound was due to asynchronous closure of the semilunar valves. Shortly thereafter Rouches[2] denied this interpretation and introduced the time-honored term "claquement d'ouverture de la mitrale" to indicate that this additional sound was associated with the opening of the mitral valve. Potain[3] drew a distinction between triple rhythm at the apex, where he thought it was caused by an opening snap of the mitral valve, and at the base, where the additional sound allegedly was due to an asynchronous closure of the semilunar valves.

With the advent of phonocardiography, Mozer and associates[4] stated that the triple rhythm in mitral stenosis was not due to an asynchronous closure of the semilunar valves but to a sound with its own individuality, similar to the physiologic third heart sound. However, the incompleteness of their study makes it difficult to accept their conclusion. In fact, in their study the phonocardiographic events were timed only with the electrocardiogram. Since it is well known that there is no necessarily consistent relationship between the mechanical and electrical events in the cardiac cycle, considerable uncertainty must shroud their conclusion. Moreover, if one keeps in mind the commonly accepted basis of the third heart sound, it is difficult to accept the suggestion that this can occur in mitral stenosis, in which the A-V flow is markedly reduced. Margolies and Wolferth,[5] in a phonocardiographic study correlated with venous and roentgenokymographic tracings, concluded that in the majority of cases one is dealing with a sound phenomenon coinciding with the opening of the A-V valves, although in some instances a reduplication of the second sound could be demonstrated.

*Present address is Michael Reese Hospital, 29th and Ellis Avenue, Chicago, Ill.
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Lian[6] believed that the apical extra sound is an accentuation of the initial part of a diastolic rumble; however, his observations are of limited value in that the acoustic phenomena were timed only with the brachial arteriogram, which is related only with difficulty to the various phases of diastole.

Finally, Duchosal[7] entertained the possibility of two different types of extra sound, one occurring at an interval of 0.05 to 0.11 second after the second sound and due to a reduplication of it, the other falling at an interval greater than 0.11 second and representing the beginning of a diastolic rumble. This study is open to criticism in that, as indicated by Burnstein[8] and Braun Menendez and Orias,[9] the duration of the isometric relaxation and rapid filling phases normally undergoes wide variations.

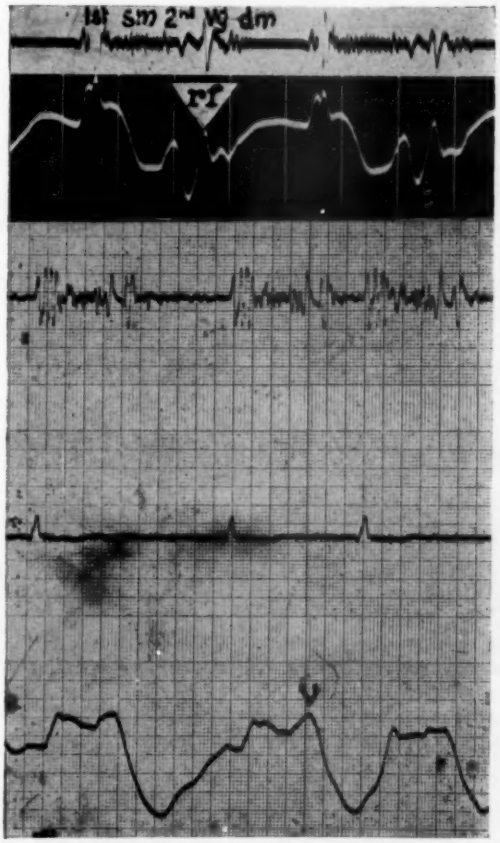

Fig. 1.—Case 1. Apical phonocardiogram recorded with apex cardiogram (Fig. 1,*A*) and with electrocardiogram and jugular tracing (Fig. 1,*B*). Note the presence of a large vibration coinciding with the peak of the wave of rapid filling of the apex cardiogram and with the descending branch of the V wave of the jugular tracing. For further details see text.

Key to abbreviations used in Figs. 1 through 5: *1*: first heart sound; *2*: second heart sound; *sm*: systolic murmur; *vg*: ventricular gallop; *dm*: diastolic murmur; *dr*: diastolic rumble; *rf*: rapid filling.

A review of 84 patients with clinical and phonocardiographic evidence of mitral stenosis revealed that in 5 cases in the precordial and apical phonocardiograms an extrasound of high intensity could be shown to coincide with the wave of rapid filling (ventricular gallop). Presentation of such cases has seemed worth

while both for the rarity of this finding and for deciding whether this extrasound is connected with a stenotic lesion of the mitral valve or with other associated valvular lesions modifying the hemodynamics of mitral stenosis.

CASE REPORTS

CASE 1.—Male, aged 52 years. He had a tonsillectomy at the age of 18 years because of repeated bouts of tonsillitis. For 6 months prior to admission he suffered from orthopnea, exertional dyspnea, nocturia, ankle edema, and upper abdominal pain. Pertinent physical findings included slight cyanosis of the lips, distention of the jugular veins which appeared to be pulsating, cardiomegaly, hepatomegaly with pulsating lower edge 5 cm. below the costal margin. Auscultation revealed a Grade 2 systolic murmur and a diastolic rumble radiating from the apex to the left axilla and midprecordium. A triple rhythm was heard over the same areas. Fluoroscopy revealed an enlarged heart shadow with a transverse diameter of 18.5 cm. and a longitudinal diameter of 19 cm. A double contour was noted on the right and there was a 2 to 3 plus left auricular enlargement. The right auricle and ventricle were considerably enlarged. The ECG revealed auricular fibrillation with an average ventricular rate of 70 per minute, right heart strain and digitalis effect. The jugular tracing (Fig. 1,*A*) revealed a systolic plateau. The apical phonocardiogram revealed a systolic murmur with vibrations of irregular frequency following a first heart sound of great intensity. The second sound was of low intensity and buried in the last vibrations of the systolic murmur. Two extrasounds followed the second sound, the first probably representing an opening snap of the mitral valve, while the second was a diastolic gallop, as shown by its coincidence with the peak of the wave of rapid filling of the apex cardiogram and with the descending branch of the V wave of the jugular tracing (Fig. 1,*A* and *B*). Low-pitched vibrations giving rise to a mid-diastolic rumble followed the last extrasound.

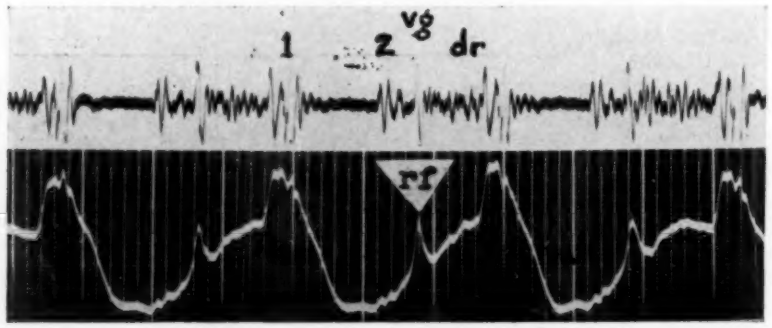

Fig. 2.—Case 2. Apical phonocardiogram with simultaneous apex cardiogram. Note the presence of a large vibration following the second sound and coinciding with the wave of rapid filling of the apex cardiogram. For further details see text.

CASE 2.—Female, aged 37 years. She had rheumatic fever at age 18 years, followed by numerous recrudescences. During the 2 years prior to admission, the patient suffered from dyspnea, weakness, palpitation, and cough, occasionally productive of bloody sputum. At physical examination, the heart was enlarged in all diameters. There was a diastolic rumble radiating from apex to left axilla and midprecordium. A booming first sound and a diastolic gallop, also, were present over the same areas. There was slight dullness and numerous moist crepitant râles over the right base posteriorly. The liver was palpated 5 cm. below the costal margin and pulsated markedly. Three plus pitting edema of the lower extremities was present. The ECG showed auricular fibrillation with an average ventricular rate of 90 per minute and right heart strain. Fluoroscopy revealed generalized cardiac enlargement with a 3 plus left auricular enlargement. The hilar shadows and the vascularity of the lung fields were markedly increased. Phonocardiogram (Fig. 2) revealed diastole to be occupied by a series of low-pitched vibrations forming a diastolic rumble. A single vibration of high intensity coinciding with the peak of rapid filling of the apex cardiogram, and therefore interpreted as a diastolic gallop, also was noted.

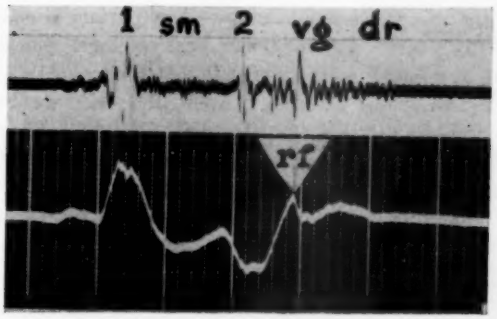

Fig. 3.—Case 3. Note the presence of a large vibration following the second sound coinciding with the wave of rapid filling of apex cardiogram. For further details see text.

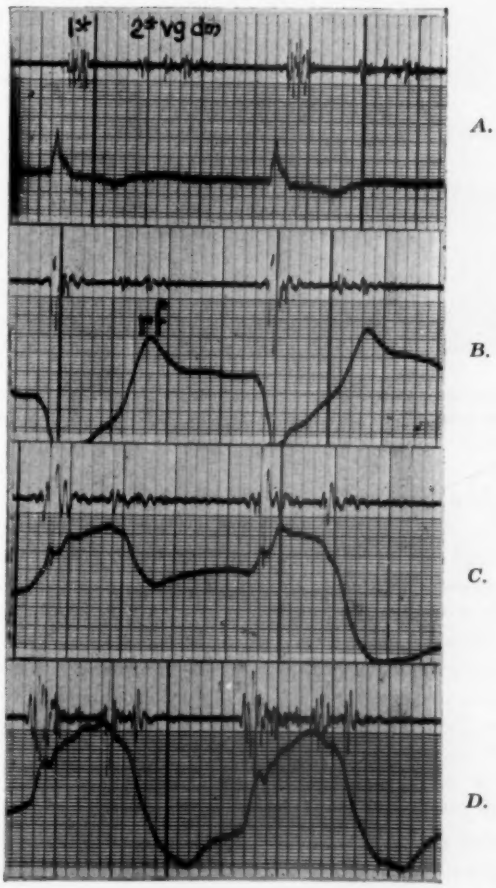

Fig. 4.—Case 4. Phonocardiogram recorded with electrocardiogram (Fig. 4,*A*), apex cardiogram (Fig. 4,*B*), jugular tracing (Fig. 4,*C*), and hepatic tracing (Fig. 4,*D*). Note the presence of a large vibration coinciding with the descending branch of the V wave of jugular and hepatic tracings and with the wave of rapid filling of apex cardiogram. For further details see text.

CASE 3.—Female, aged 43 years. She was admitted to hospital because of symptoms compatible with embolism to the middle cerebral artery. The patient was known to have had rheumatic heart disease for many years. Pertinent physical findings included the heart slightly enlarged to percussion with an apical diastolic thrill. Auscultation revealed a Grade 2 apical systolic murmur followed by a diastolic rumble. The jugular veins were distended and presented systolic pulsations. The liver was large and pulsating. The ECG showed auricular fibrillation with a moderately fast ventricular rate, vertical position, and occasional premature ventricular beats. The phonocardiogram (Fig. 3) revealed a systolic murmur, a mid-diastolic rumble, and a vibration of high intensity, coinciding with the wave of rapid filling of the apex cardiogram.

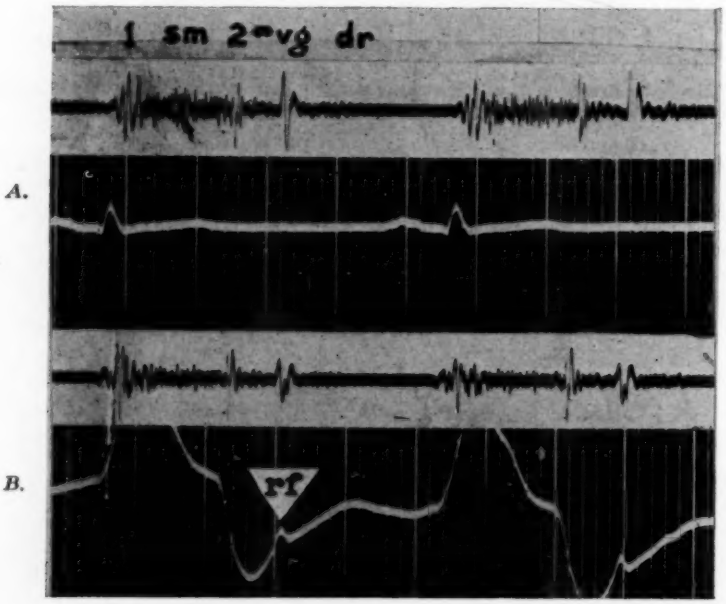

Fig. 5.—Apical phonocardiogram (*B*) recorded with the electrocardiogram (upper tracing, *A*). Note the presence of a large vibration coinciding with the wave of rapid filling of the apex cardiogram. For further details see text.

CASE 4.—Female, aged 64 years. Eight years prior to admission a cerebral vascular accident resulted in left hemiplegia. She had been on digitalis ever since. For the preceding 2 years she suffered from dyspnea, cough, palpitations, nocturia, and progressive swelling of the ankles. At physical examination the heart appeared to be enlarged in all diameters; an apical systolic murmur and a mid-diastolic rumble were heard. Both lung bases were dull and presented numerous moist crepitant râles. The liver was palpated 6 cm. below the costal margin and was smooth and tender. The jugular veins were distended and pulsating. At fluoroscopy there was generalized cardiac enlargement, left auricular enlargement +++, and marked congestion of both lung bases. The electrocardiogram showed auricular fibrillation with an average ventricular rate of 74 per min. and digitalis effect. Both jugular and hepatic tracings (Fig. 4, *C* and *D*) showed systolic plateau. The phonocardiogram (Fig. 4) revealed a systolic murmur and a mid-diastolic rumble. Between the second sound and the beginning of the diastolic rumble a vibration of high intensity and coinciding with the wave of rapid filling of the apex cardiogram was noted.

CASE 5.—Male, aged 18 years. He had rheumatic fever at the age of 10 and suffered from occasional dyspnea, palpitations, weakness, cough, and epigastric discomfort ever since. During the 6 months prior to admission these symptoms became progressively worse. Physical examination revealed slight cyanosis of the lips and cheeks. The jugular veins were markedly engorged. The left heart border was in the sixth intercostal space in the anterior axillary line. On auscultation a Grade 2 apical systolic murmur, a mid-diastolic rumble, and a diastolic gallop rhythm were

noted. A short early diastolic murmur interpreted as a Graham Steell murmur was heard at Erb's point. Fluoroscopic examination revealed marked cardiac enlargement. Inflow and outflow tracts of the left ventricle were enlarged, as were the pulmonary artery and the outflow tract of the right ventricle. The ECG showed sinus rhythm P mitrale and a tendency to low voltage. The phonocardiogram (Fig. 5) revealed a systolic murmur occupying the entire period of systole. The second sound was followed by an extrasound of high intensity, coinciding with the wave of rapid filling of the apex cardiogram. The base line was distorted in mid-diastole by low pitched vibrations, forming a mid-diastolic rumble.

On the seventh day the patient had an attack of severe dyspnea and chest pain and died suddenly. Autopsy revealed cardiomegaly (440 Gm.) with generalized cardiac enlargement, but especially left auricular enlargement. The mitral orifice was markedly dilated (13.8 cm.^{2}) with thickened valvular leaflets. The chordae tendineae were thickened and shortened. An embolus of recent origin occluding the main branch of the left pulmonary artery was found. Anatomic diagnoses were: embolus occluding the main branch of the left pulmonary artery; rheumatic endocarditis of the mitral valve, resulting in pure mitral insufficiency; chronic passive congestion of the organs.

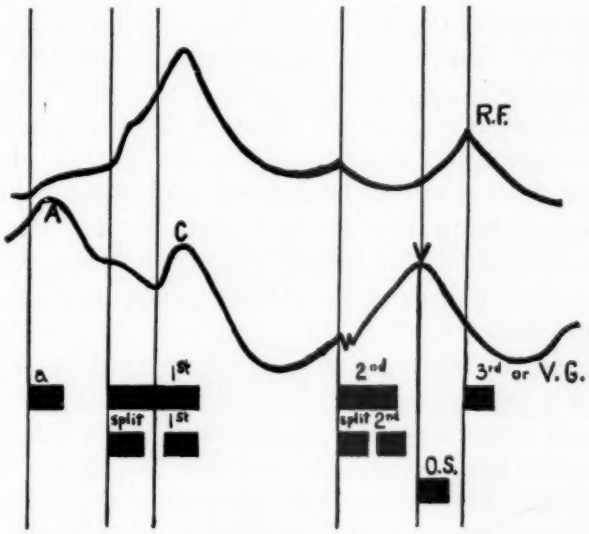

Fig. 6.—Diagram illustrating the time relationships of the different elements of the apex cardiogram (upper tracing), jugular phlebogram (middle tracing), and phonocardiogram. *R. F.*: wave of rapid filling; *A, C, V*: positive waves of the venous pulse; *1, 2, 3*, and *a*: heart sounds; *V. G.*: ventricular gallop; *O. S.*: opening snap.

DISCUSSION

Gallop rhythm is a particular cadence due to the addition of 1 or 2 diastolic sounds to the usual 2 heart sounds. There are essentially 3 types of gallop rhythm: (a) atrial type in which the extrasound occurs at the time of auricular contraction; (b) diastolic or ventricular type in which the additional sound falls in early diastole at the time of rapid filling; (c) summation type resulting from the fusion of previous 2 extrasounds when diastole is very short because of a rapid ventricular rate or a long P-R interval. The ventricular type of gallop rhythm may be confused with a widely split second sound or an opening snap of the mitral valve. The former is clinically recognizable by its close relation

to the second sound and its maximum intensity over the base. The latter is heard only in mitral stenosis and is clinically recognized by its close association to the second sound and by its lower pitch. Like the ventricular gallop, it is best heard over the apex. Clinically the ventricular gallop is recognized, unless the rate is very rapid, by its fairly wide separation from the second sound, its apical location, and its higher pitch and intensity in comparison with the opening snap of the mitral valve. Not infrequently in mitral stenosis one is unable to distinguish clinically among these 3 types of triple rhythm, and graphic methods of proof must be used. An illustration of sound and mechanical phenomena for these 3 types of triple rhythm is given in Fig. 6. From this it can be seen that the ventricular type of gallop is characterized by its coincidence with the wave of rapid filling of the apex cardiogram and with the descending branch of the *V* wave of the jugular tracing.

The third heart sound is commonly defined as a sound produced by vibrations of the ventricular wall which are produced by the impact of the blood column during the phase of rapid filling.[10] Although the more intimate mechanism by which the ventricular gallop is produced is still the object of debate, there is general agreement in considering this phenomenon as an exaggeration of the physiologic third heart sound.[11] It must then be assumed that the physiologic bases for its occurrence are either an increase in the amount or rapidity of the A-V flow, or changes in the elasticity of the ventricular wall.

In mitral stenosis due to decrease in mitral area, the amount of blood flow during the phase of rapid filling is diminished. Consequently, it is difficult to believe that in this condition a ventricular gallop, at least originating in the left ventricle, could exist.

As demonstrated by the systolic expansile pulsations of the jugular veins and liver, the first 4 cases above had tricuspid insufficiency in addition to mitral stenosis. It is known that whenever insufficiency of the A-V valves occurs, and this includes tricuspid insufficiency, the A-V flow increases. One can speculate, therefore, that in this case the gallop may originate in the right ventricle. Superficially, it would appear contradictory that in our patient the ventricular gallop was heard best over the left precordial and apical region. However, we know from fluoroscopic and angiocardiographic studies that the right ventricle occupies a great part of the frontal projection of the cardiac silhouette. Moreover, it is known that dilatation of the right ventricle causes it to rotate clockwise and move cephalad and anteriorly. Consequently, it can be understood that a gallop originating in the right ventricle may be heard best over the left anterior chest wall. Case 5 presented a rheumatic valvulitis of the mitral orifice giving rise to pure insufficiency. The diastolic rumble was functional and indicated a relative stenosis caused by marked dilatation of the left auricle. Similar auscultatory findings, simulating a stenotic lesion of the mitral valve, have been studied by Bland and associates[12] and Luisada.[13] As discussed above, the increased A-V flow associated with mitral insufficiency undoubtedly was responsible for the ventricular gallop in this case.

In an extensive study on mitral stenosis, Wood[14] recently stated that the true ventricular gallop does not occur in the pure form of this disease, but is

found only when a significant degree of mitral insufficiency also exists. Our experience confirms this statement in that the only cases with proved ventricular gallop also had other associated valvular deformities. In 4 of the cases reported above, tricuspid insufficiency existed, also, in addition to mitral stenosis. In Case 5, despite characteristic auscultatory findings, there was no mitral stenosis, but only pure mitral insufficiency.

It would therefore seem that the occurrence of a true ventricular gallop in cases of mitral stenosis should make one suspect the existence of other valvular abnormalities, especially tricuspid insufficiency.

SUMMARY

Eighty-four cases of mitral stenosis were studied for the occurrence of true ventricular gallop. Five cases of this type of triple rhythm were discovered and the true nature of the gallop was proved by simultaneous phonocardiograms, apex cardiograms, and jugular tracings.

Of these 5 cases, 4 had associated tricuspid insufficiency, and 1 did not have mitral stenosis, but pure mitral insufficiency.

The mechanism of ventricular gallop and the distinction between other forms of triple rhythm is discussed with emphasis placed on mitral stenosis.

It is concluded that the occurrence of ventricular gallop in mitral stenosis should alert one to the likelihood of the existence of other valvular abnormalities.

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THE ELECTRICAL MANIFESTATIONS OBSERVED IN DAMAGED OR INJURED CARDIAC MUSCLE. AN EXPERIMENTAL STUDY

V. ALZAMORA-CASTRO, M.D., GUIDO BATTILANA, M.D., AND RICARDO ABUGATTAS, M.D.

LIMA, PERU

SINCE the outstanding work of Frank N. Wilson[1-3] and his associates in relation to the currents of action and injury in the cardiac tissue, many important contributions have advanced the knowledge of the electrical manifestations produced in the damaged or injured cardiac tissue.[4-16] Most of the previous conclusions have been confirmed but the method used in the experiments herein described permits the different origin of the monophasic action potentials to be clearly understood, and also facilitates the observation of the multiple electrocardiographic changes produced by progressive damage of the cardiac muscle.

METHOD

The method used in some experiments has been described previously.[15,16] Sixty-two experiments were performed in 30 dogs. Observations were made after splitting the sternum and opening the pericardial sac. In most instances saline solutions of 2.5 or 5 per cent cocaine hydrochloride, or 5 per cent solutions of KCl or 20 per cent solutions of magnesium sulfate were injected into the anterior descending coronary artery, or one of its branches, until monophasic action potentials were recorded in the ventricular area supplied by the vessel.[16] In 3 instances cocaine solutions were injected into the artery and immediately afterward solutions of KCl were injected through the same needle. In 6 experiments a large coronary artery was ligated and unipolar epicardial leads taken from the ischemic zone. In 5 instances saturated solutions of KCl were poured over the epicardial surface in the immediate neighborhood of the epicardial exploring electrode.

Records were obtained with Sanborn Twin-Beam or Twin-Viso electrocardiographs connected to the animal through the D.-C. amplifier. One terminal was connected to the right hind leg through a nonpolarizable electrode and the other terminal was connected to the exploring electrode through a similar nonpolarizable boot.[15,16] In some experiments an olive-shaped electrode was introduced into the ventricular cavities, the indifferent electrode being attached to the left hind leg. In most experiments the unipolar epicardial lead was taken simultaneously with Lead II. In the great majority of the experiments records were taken at short intervals while the epicardial electrode remained immobile. There were instances in which the epicardial electrode was moved slowly from the most damaged zone towards the normal muscle. When toxic substances were injected into the coronary arteries, or when this vessel was ligated, tracings were taken while electrocardiographic changes progressed.

From the Department of Cardiology, Hospital Dos de Mayo, University of San Marcos Medical School, Lima, Peru.

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RESULTS

When saline solutions of cocaine were injected into the coronary artery, in the ventricular area supplied by the vessel, monophasic action potentials were obtained but no currents of injury were observed (Fig. 1). In some of these experiments slight upward displacements of the isoelectric line were seen while the monophasic waves were recorded, and in other instances minor downward displacements of the same line were present a few minutes after the injection.

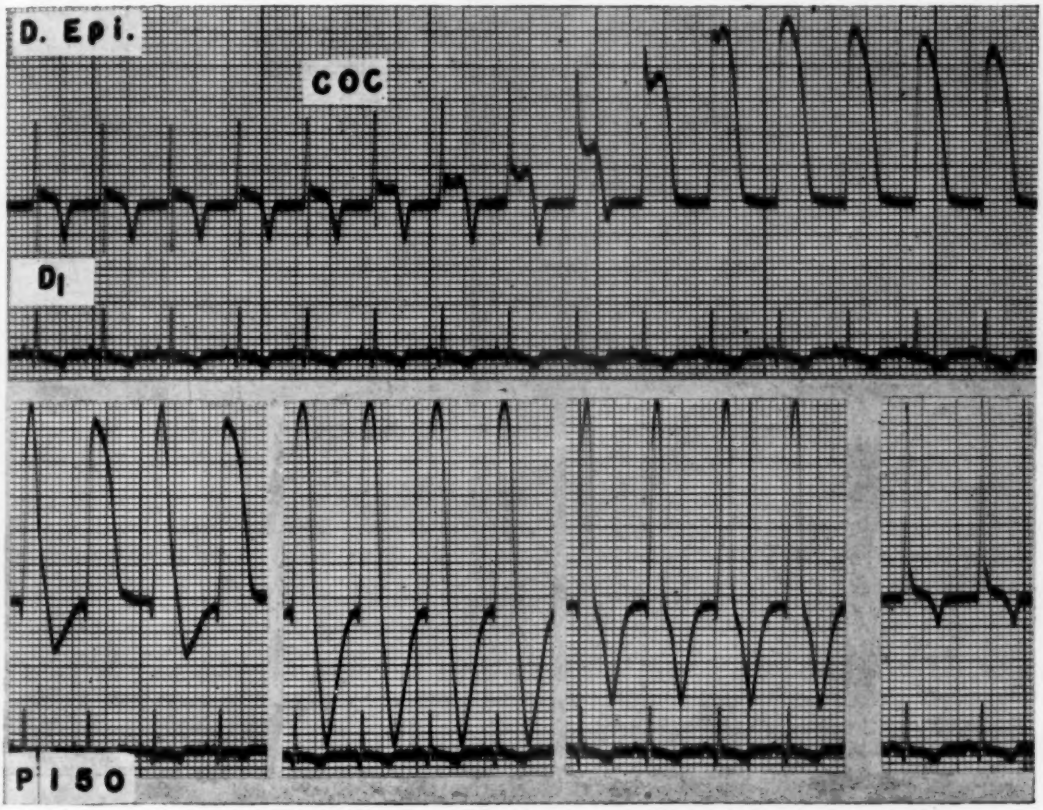

Fig. 1.—After injecting a solution of cocaine hydrochloride into the coronary artery, striking electrocardiographic changes are seen in the ventricular area supplied by this vessel. In the direct unipolar epicardial lead, monophasic action potentials are obtained in absence of currents of injury. The small negative deflection preceding the monophasic wave is due probably to the unbalanced negative cavitary potentials. When damage is less marked, QRS-T complexes abnormal in size and width are recorded; as the damage diminishes, the excitatory process progresses more rapidly and finally the normal tracing reappears. The damage produced by cocaine is local since no changes are recorded in Lead II.

In the experiments in which records were taken before, during, and after a saturated solution of KCl was poured under the epicardial exploring electrode, the plateau of the monophasic component or the monophasic wave remained at the level of the preinjury isoelectric line (Fig. 2).

In all experiments, when a 5 per cent solution of KCl was injected into the coronary arteries, the monophasic wave overshot the preinjury isoelectric line (Fig. 3).

The injection of cocaine produced monophasic action potentials without injury currents but, if in such circumstances an injection of KCl was given through the same needle, monophasic waves continued being recorded. However, a downward displacement of the isoelectric line was observed (Fig. 4).

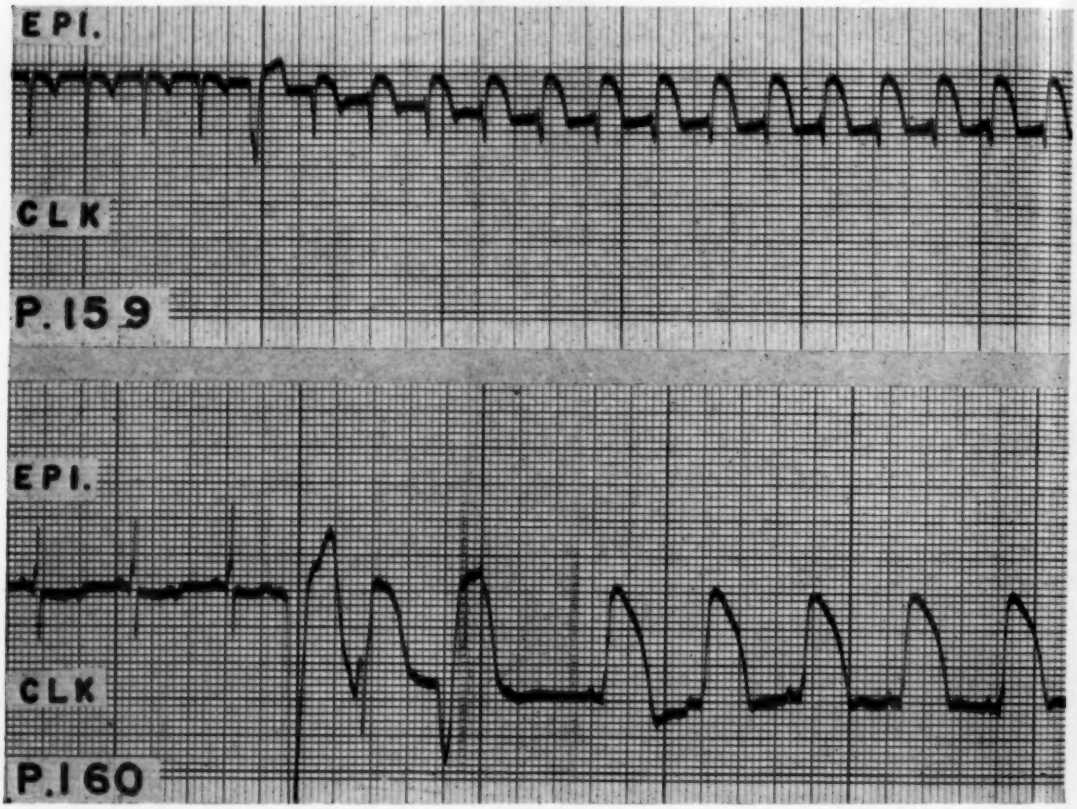

Fig. 2.—The upper record is the direct unipolar epicardial lead taken over the surface of the right ventricle; the lower record was obtained over the surface of the left ventricle. In both instances a saturated solution of KCl was poured underneath the exploring electrode. The monophasic component does not overshoot the preinjury isoelectric level.

In the unipolar epicardial leads, when solutions of magnesium sulfate were injected into the coronary arteries, an upward displacement of the isoelectric line was observed while positive RS-T displacements were being recorded (Fig. 5). Magnesium sulfate is apt to produce ventricular fibrillation and this is probably the reason why we were unable to obtain pure monophasic action potentials.

When toxic substances were injected into a large coronary artery, and the epicardial and endocardial electrodes placed opposite each other in the ventricular wall, similar electrocardiographic changes were recorded in both leads. This fact strongly suggests transmural damage. The striking variations in the epicardial leads and the absence of electrocardiographic changes in Lead II (Figs. 1 and 3) demonstrated that the injection of toxic substances produced only local damage. The electrocardiographic abnormalities produced by cocaine lasted on an average of 20 minutes. The damage determined by KCl or magnesium sulfate

disappeared more rapidly. When an injection of toxic susbtances was given into a coronary artery, an invariable sequence of electrocardiographic changes was observed. After the monophasic waves, abnormal QRS-T complexes were recorded while their width and size gradually diminished until the normal electrocardiogram reappeared (Figs. 1 and 3). Similar electrocardiographic manifestations could be observed early after the injection when the epicardial electrode was slowly moved from the place in which monophasic action potentials were present toward the normal muscle.[16]

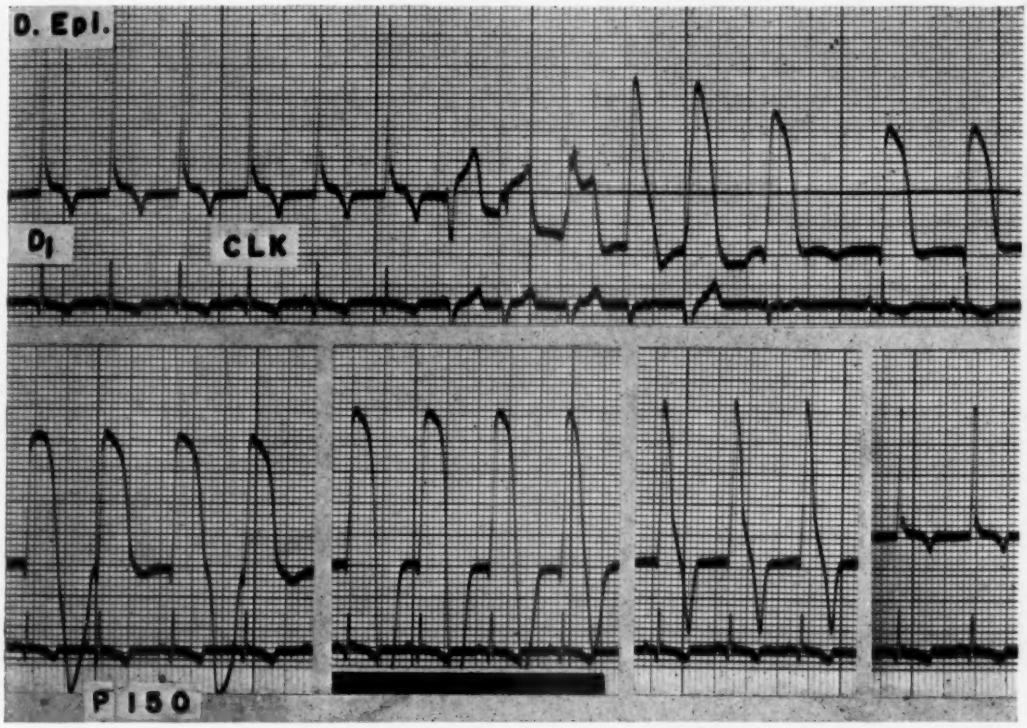

Fig. 3.—A unipolar direct epicardial lead and Lead II were taken simultaneously. A solution of 5 per cent of KCl was injected into the coronary artery. The electrocardiographic changes recorded during this experiment were similar to those obtained in the same dog when a solution of cocaine was injected (Fig. 1). The only important difference is the presence of currents of injury in this case; the plateau of the monophasic wave overshoots the preinjury isoelectric line.

In the direct epicardial unipolar leads taken during ligation of a large coronary artery, the QRS-T changes were very similar to those obtained in the experiments in which solutions of cocaine or KCl were injected into the coronary arteries (Fig. 6). If the epicardial electrode was moved over the ischemic zone, tracings indicating different degrees of damage were recorded. A downward displacement of the isoelectric line indicated that the current of injury was greatest in the most damaged region. In all instances in these experiments the summit of the monophasic component rose above the isoelectric level. In two instances it was evident that after ligation of the coronary artery, the primary T-wave changes were the first demonstrable electrocardiographic manifestation of damage.[6]

DISCUSSION

If we adopt the language of the membrane theory we may say that when the muscle tissue is damaged without altering the resting membrane potentials, currents of injury are not present and the monophasic wave is due solely to block of the excitatory process. Curves of this type have been recorded by Ashman and Woody[5] from the uninjured turtle ventricle. In the mammalian heart monophasic action potentials are easily produced by cocaine[16] (Fig. 1). Conversely, if in the injured muscle the resting membrane potentials are zero, or a fraction of the normal value near zero, the monophasic action current will rise from the level of the current of injury to the isoelectric line (Fig. 2). Curves of this kind have been previously recorded by Nahum, Hamilton and Hoff.[14] When in the damaged zone the membrane is not completely depolarized, as probably occurs with weaker solutions of KCl or in the ischemic tissue, the summit of the monophasic action potentials will rise above the isoelectric level (Fig. 3). In these circumstances it could be assumed that the partially depolarized muscle does not respond to the excitation wave.[12,13] In other words, the part of the monophasic wave that overshoots the isoelectric level may be explained as a "cocainic effect." The overshooting may be explained also by a reversal of polarization during excitation, as the experiments of Cole and Curtis[17] would suggest, but the injury of the cell by a capillary electrode may determine partial depolarization of the membrane. A reversal of polarization is difficult to conceive in some experiments described here.

The experiments with magnesium sulfate suggest that in the damaged zone the resting membrane potentials are supernormal (Fig. 5). We do not know at present, but we may infer, that in pathologic situations a number of toxic substances are damaging the cardiac muscle; consequently, many of the possibilities mentioned may be participating.

The experiments in which the effects of cocaine and KCl are combined (Fig. 4) prove that in recording action potentials the only essential condition is block of the excitation wave in the damaged zone; currents of injury may or may not be present.

The RS-T displacements have been considered, with reason, as the most relevant manifestation of injury. In the damaged muscle Bayley[7] clearly distinguished between the injured and the ischemic zones on the basis of the electrical effects produced by each. The injured zone is responsible for the RS-T displacements and the ischemic region accounts for the primary T-wave changes. In this manner Bayley defined the two extremes of the electrical manifestations observed in the damaged zone. Nevertheless, as Wilson, Johnston and Hill,[2,3] Sodi-Pallares,[8] and others have pointed out, in the electrocardiograms from the injured or damaged zones there are some QRS-T changes that are not clearly understood.

When toxic substances are injected into the coronary arteries, it may be supposed that large islands of cardiac muscle are more or less uniformily damaged. If damage disappears in a short interval of time, as is the case with the injections of cocaine or KCl, the electrocardiographic changes observed during the experiments will represent different degrees of damage. In these instances it was

evident that in the damaged zone, between the pure monophasic waves and the minimal electrocardiographic changes observed before normal activation reappears, there are a series of curves indicating different degrees of damage or different degrees of block. When block is severe, monophasic action potentials are re-

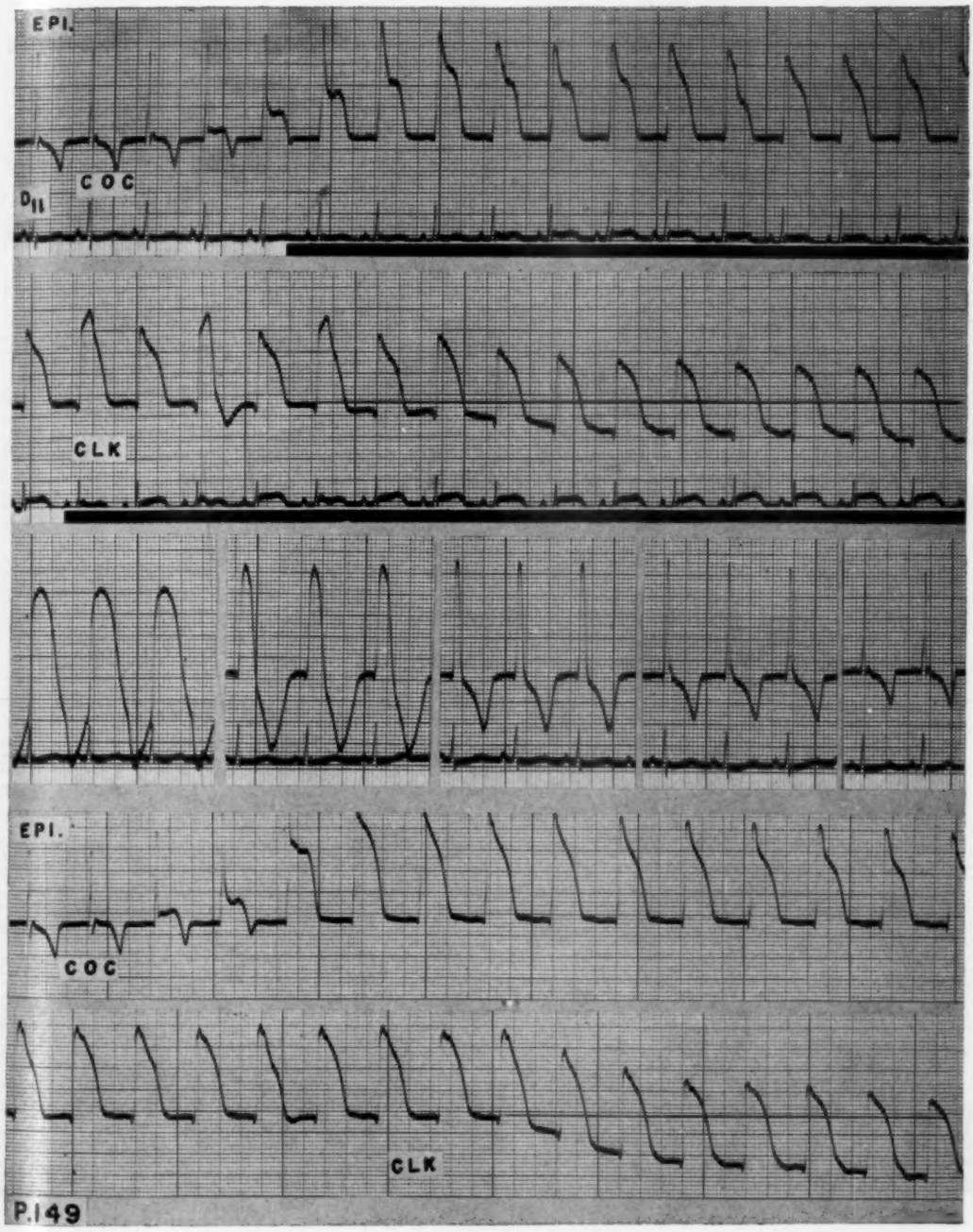

Fig. 4.—In two experiments performed in the same dog, the injection of a solution of cocaine determined monophasic action potentials without currents of injury. As soon as a solution of KCl was injected through the same needle a downward displacement of the isoelectric line was evident.

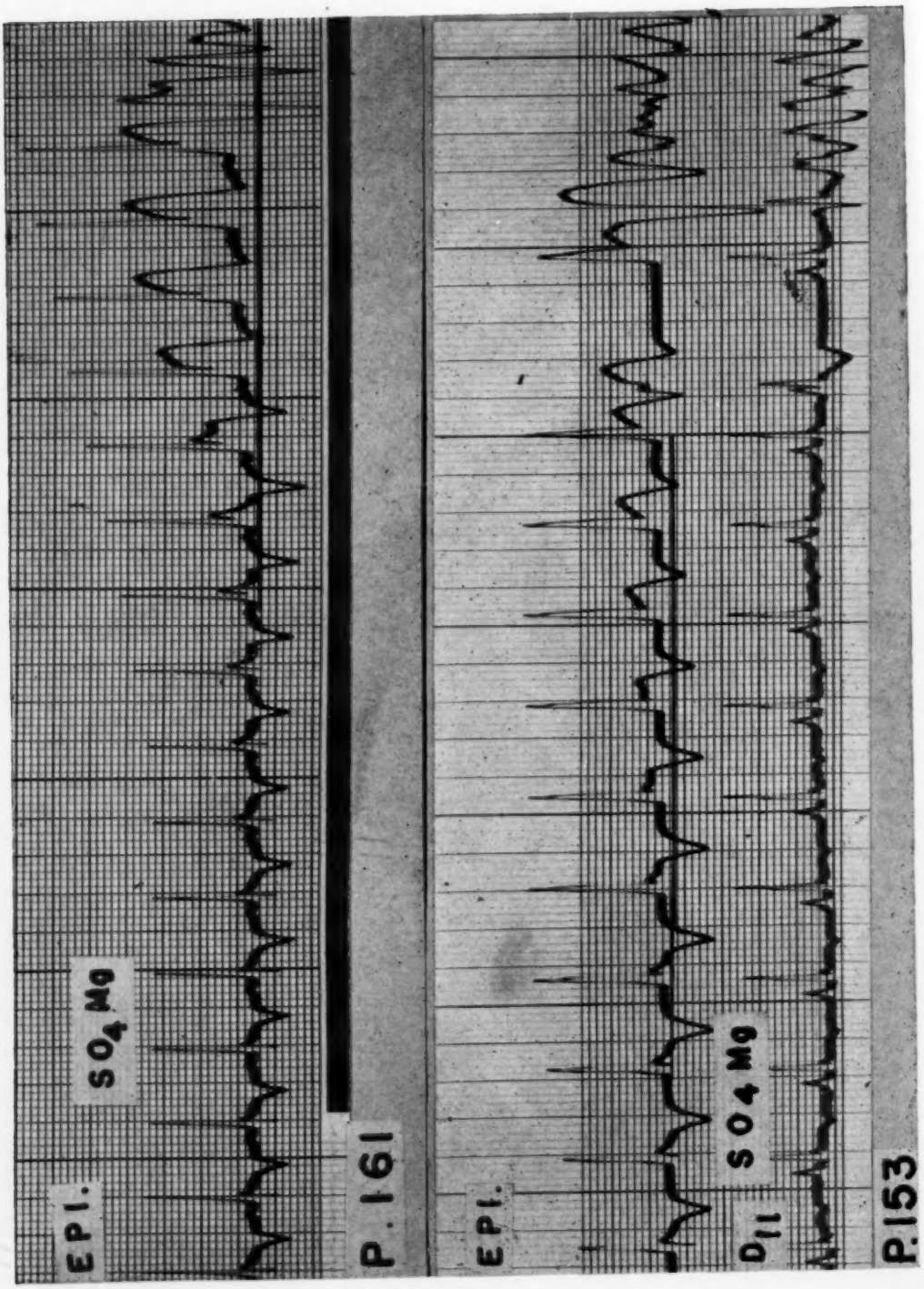

Fig. 5.—A 20 per cent solution of magnesium sulfate was injected into the coronary arteries in 8 dogs. In all instances an upward displacement of the isoelectric line was observed while positive RS-T displacements were being recorded.

corded. When damage is less marked, the size and width of the abnormal QRS-T complexes clearly indicate that depolarization and repolarization are progressing slowly. As the damage diminishes the excitatory process is accomplished more rapidly and finally the normal curve reappears (Figs. 1 and 3). The foregoing electrocardiographic changes have been obtained invariably in a great number of experiments with cocaine, KCl, and other substances not mentioned here.

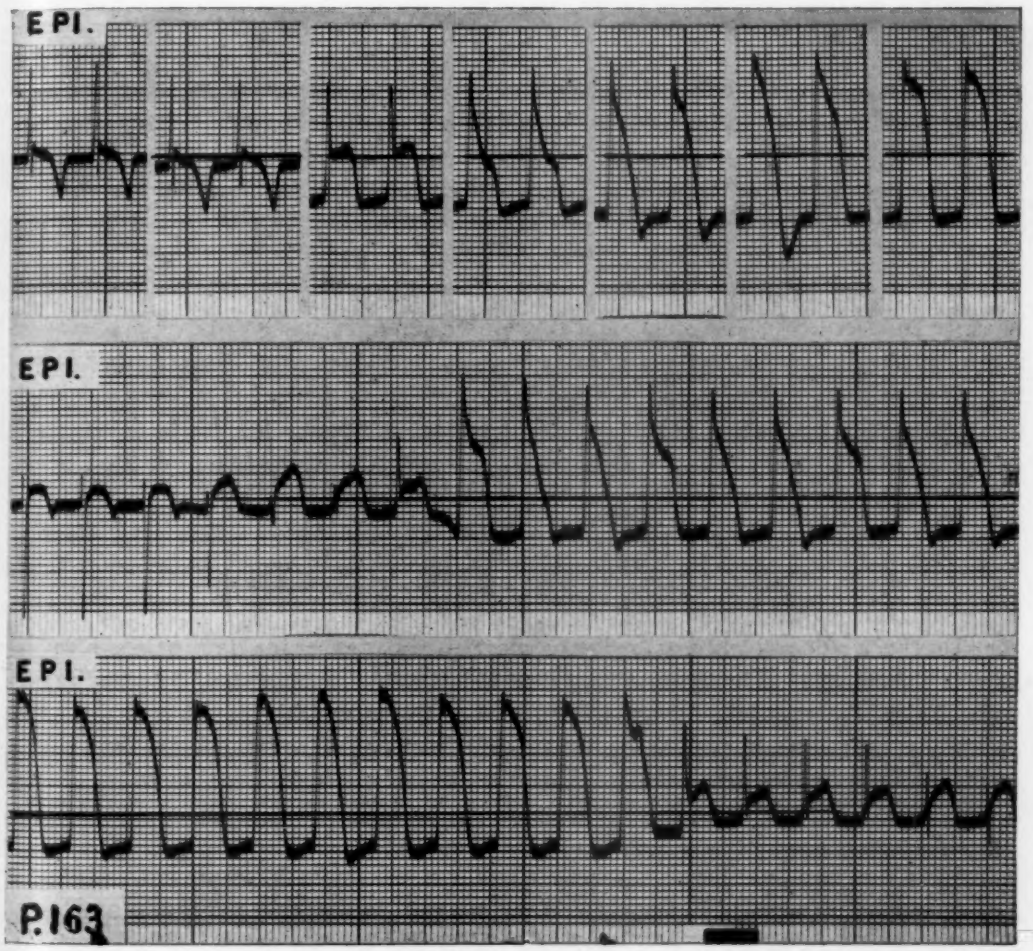

Fig. 6.—After ligation of a large coronary artery, the QRS-T changes were found to be similar to those recorded after the injection of toxic substances into the coronary arteries. (See Figs. 1, 3, and 4.) In this figure the upper tracings were obtained at intervals after ligation of the anterior descending coronary artery. The medium and lower tracings were recorded while the exploring electrode was moved from the most damaged toward the less damaged zones. In all instances currents of injury were evident over the damaged zone.

Tracings obtained from an ischemic island produced by ligation of a coronary artery were also similar (Fig. 6). In two experiments of this kind it was evident, as Bayley, La Due and York[7] observed, that the primary T-wave changes were the first demonstrable electrocardiographic sign of damage. It is important to mention here that in the damaged zone *pari passu* with the degree of block there is an impairment of the contractile activity of the cardiac muscle (Alzamora-Castro and associates[18]).

Uniformly damaged zones are probably rare; consequently, the sequential electrocardiographic changes observed during these experiments in a period of time, while the exploring electrode remains in place, must be similar to the tracings that could be recorded in the regions surrounding the most severely damaged zone. Actually, when the epicardial exploring electrode is moved from the most damaged region towards the normal muscle, the electrocardiographic changes are comparable to those recorded in situ during the time severe damage disappears. Accordingly, if there is an island of damaged muscle, particularly if semidirect leads are employed, the resulting electrocardiogram will be composed of a series of curves, each representing a different degree of block or a different degree of damage. In this manner not only the RS-T displacements, but also the increase of voltage of the R wave, the delay of the intrinsic deflection, the changes in the T waves, the duration of the electrical systole, etc., observed in the electrocardiograms taken from the injured or damaged zones can be explained satisfactorily.

If these experiments are repeated in hearts in which bundle branch blocks have been produced, the electrocardiographic changes are similar.[18] This fact strongly suggests that block of the excitatory process in the muscle fiber is the main cause of the electrical manifestations described here. It could be coincidental, but the tracings recorded when damage is not severe recall those observed in ventricular hypertrophies and other pathologic conditions in which the cardiac muscle is compromised.[15]

SUMMARY

The electrical manifestations produced in the cardiac muscle by ischemia and toxic substances have been studied.

In the damaged cardiac muscle the resting membrane potentials may be zero, subnormal, or supernormal. Damage producing block of the excitation wave may be observed without altering the resting membrane potentials. Accordingly, monophasic action potentials may be observed with or without currents of injury, and even with currents of injury, against the rule. In recording monophasic waves the only essential condition is block of the excitation wave. The presence or absence of injury currents is immaterial.

In the damaged cardiac muscle the excitation wave is blocked. The intensity of block varies with the degree of damage. When block is severe, the excitation wave does not progress in the damaged tissue and monophasic action potentials are recorded. When block is less marked, the depolarization and repolarization processes are progressing slowly, and, thus, QRS-T complexes abnormal in size and width are registered. In the less damaged zone only the recovery process is delayed and primary T-wave changes recorded.

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ATRIAL VAGAL ESCAPE AFTER CRUSHING PARTS OF THE SINUS NODE

D. Scherf, M.D., S. Blumenfeld, M.D., D. G. Chamsai, M.D., E. C. Reid, M.D.,* and A. Weisz, M.D.

New York, N. Y.

WE PREVIOUSLY reported a form of vagal escape of the atria of the dog's heart, as seen after crushing parts of the sinus node by applying a surgical clamp across this structure.[5] In 14 of 26 experiments, after the clamping, faradic stimulation of the right vagus in the neck slowed, but did not stop, the atrial activity, while in 8 other experiments the rate remained unchanged, even when the strongest faradic current was used. In only 4 experiments did stimulation of the vagus lead to the usual inhibition of the whole heart; this happened in animals whose hearts were in poor condition, flabby and dilated due to asphyxia or pneumonia. These effects of crushing appeared as soon as the clamp was applied and lasted up to 29 minutes after removal of the clamp.

This investigation was extended, and in the experiments described below the clamps were applied more systematically.

METHOD

Eighteen dogs weighed between 9.5 and 14 kilograms. After instituting artificial respiration, the chest wall and the pericardium were opened and the vagi dissected and severed in the neck. The first clamp was applied across the lower end of the sinus node just above the inflow of the inferior vena cava. The subsequent clamps were placed just above the first one. As in the previously reported experiments, no attempt was made to clamp off the sinus node completely, so that the upper part of the node remained functioning. In some of the dogs care was taken to avoid clamping the artery ascending on the right lateral wall of the atrium and supplying the sinus node, but the results were the same. Sometimes A-V rhythm appeared temporarily, but this is not significant since any sudden irritation of even a small part of the sinus node may occasionally lead to transient sinus block.[3] The right vagus nerve was stimulated with a Cambridge inductorium; electrocardiograms were registered in Lead II.

RESULTS

In 8 experiments, after application of 2 or 3 clamps at the lower end of the sinus node, stimulation of the right vagus did not inhibit the atrial activity. We then applied the clamps above each other after atrial vagus escape had appeared.

From the Department of Medicine, New York Medical College.

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*Trainee of the National Heart Institute.

The results are best illustrated by Figs. 1 and 2 which were obtained in typical experiments. Before application of the clamps, vagal stimulation causes typical standstill of both atria and ventricles (Fig. 1, *A*). The second P wave after the end of vagal stimulation shows the effect of strong vagal stimulation. This is the characteristic shortening of the depolarization time evidenced in the electrocardiogram by shortening of the P wave and depression of the T_P wave, which appears as an inverted part of the P wave proper.[4] After application of the first clamp over the lower aspect of the sinus node, the effect of vagus stimulation is essentially the same: a long standstill of the whole heart is followed by an atrial and ventricular escape (Fig. 1, *B*). After application of the second clamp, an A-V rhythm appears temporarily alternating with sinus rhythm. Stimulation of the right vagus nerve slows the atria markedly and causes partial A-V block but does not lead to complete inhibition as it did previously (Fig. 1, *C*). After placing of the third clamp, the sinus rate increases slightly (Fig. 1, *D*) and is now uninfluenced by vagus stimulation. Fig. 1, *E* was taken one minute later; the sinus rate has slowed down and is still unaffected by stimulation of the vagus.

The results were the same regardless of which vagus was stimulated, but routinely only the right one was stimulated.

The same results were obtained in 8 experiments. It was decided then to continue applying the clamps one above the other after the phenomenon of atrial vagus escape had appeared. Fig. 2 shows the results obtained in such an experiment. In Fig. 2, *A* faradic stimulation of the right vagus before placing the clamps results in the usual standstill. Again no difference was seen after placing the first clamp across the lower end of the sinus node (Fig. 2, *B*).

After application of the second clamp, the right vagus was stimulated again for a shorter time than before, and once more complete standstill resulted (Fig. 2, *C*). An atrial extrasystole appeared after the stimulation ended, a common phenomenon. After application of the third clamp, vagus stimulation caused only a slowing of the atrial rate from 214 to 150 beats per minute but no standstill appeared (Fig. 2, *D*). Again the typical changes of the P waves appeared during vagal stimulation. A fourth clamp was now applied above the third one, and during vagus stimulation there was again complete standstill of the heart (Fig. 1, *E*). Fig. 2, *F* was obtained 26 minutes after the removal of all the clamps. The P waves had become inverted. This time vagus stimulation again did not affect the atrial rate but caused complete A-V block. This effect was seen in all experiments for 15 to 30 minutes after removal of all the clamps.

In one experiment the atrial escape appeared with the application of the first clamp at the lowermost aspect of the sinus node, whereas in another experiment this phenomenon developed only after the fourth clamp was placed above the middle of the node.

In all experiments the P waves during the vagal escape resembled those of the preceding sinus rhythm; if changes occurred in the P waves of the rhythm before vagus stimulation, the same changes were visible during the stimulation.

The only difference in the P waves before and during vagal stimulation were the typical alterations described above, which were due to the vagal effect.

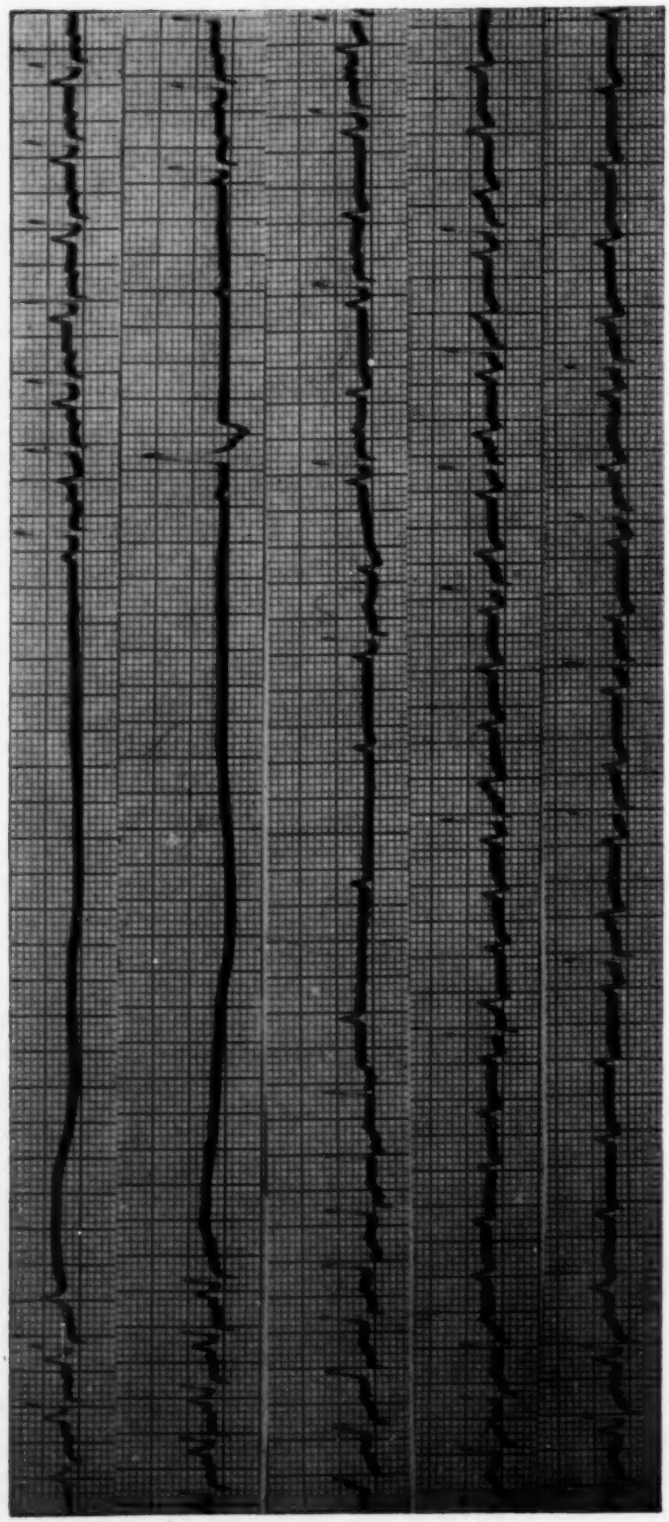

Fig. 1.—*A* shows the typical inhibition of the heart during faradic stimulation of the right vagus nerve in the neck; this effect persisted after application of a surgical clamp across the lower end of the sinus node (*B*). After application of a second clamp above the first one, vagus stimulation slows but does not stop atrial activity (*C*). A third clamp is applied above the two previous ones; the atrial activity is not influenced by the vagus stimulation with respect to rate. The P waves show by the appearance of a short and depressed T_P that the vagus effect on the atria is otherwise strong. *E*, obtained one minute later, shows essentially the same findings with a slower atrial rate.

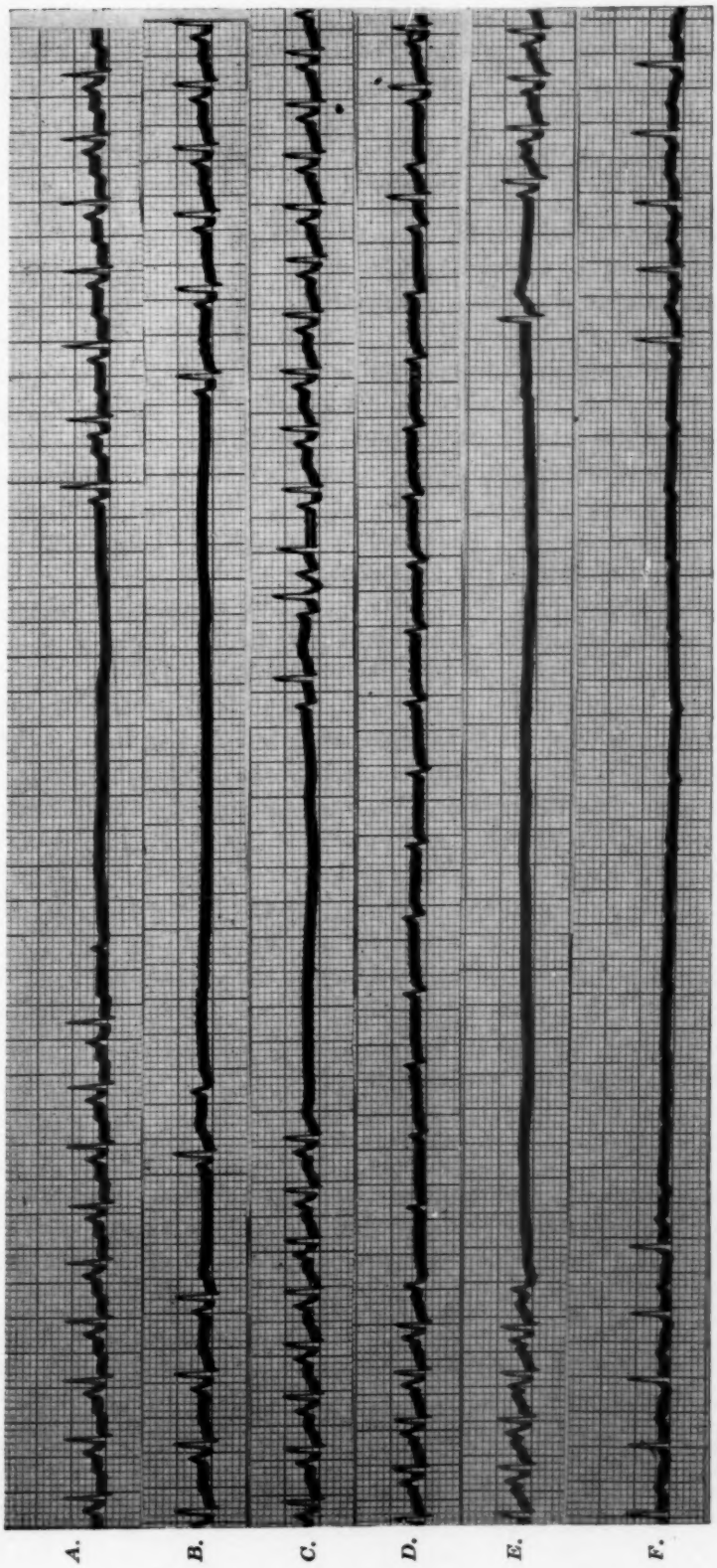

Fig. 2.—*A*, obtained before clamping, shows the typical inhibition of the whole heart during faradic stimulation of the vagus; no changes appear after a clamp is applied across the lower end of the sinus node (*B*); a second clamp is placed above the first one and the inhibition of the heart during vagus stimulation, which in this instance lasted a shorter time, is the same (*C*). After the application of a third clamp, the atrial activity slowed down during vagus stimulation but no standstill of the atria was obtained (*D*). After application of a fourth clamp above the third one, the normal vagal effect on the atria reappeared (*E*). The clamps were removed and the P waves were negative 26 minutes later (*F*). A repetition of the vagus stimulation did not influence the atrial rate

In 4 experiments in which the animal struggled in the beginning because of a prolonged excitement phase or in which asphyxia existed due to pulmonary disease, vagus stimulation after application of each of the 4 clamps caused only the typical inhibition of the atria.

DISCUSSION

The tracings of Figs. 1 and 2 show that the atria were under strong vagal influence during stimulation of the right vagus nerve.

The question arises as to why the sinus rhythm is not inhibited by the vagus stimulation after application of the clamps. One possibility would be the inability of damaged pacemaker fibers to respond in a normal way to acetylcholine. But why is the response restored when a further clamp is applied? Another possibility would be the absence of formation of acetylcholine due to the crushing by the clamps of vagus nerves running to specialized tissue of the sinus node. This would be in effect a denervation of the sinus node. This possibility has some anatomic data to support it. It is known that vagal fibers approach the right atrium in 1 or 2 branches in the area which was clamped.[1,2] In the cat, one large vagus branch runs over the azygos vein and reaches the right heart in the sulcus between the pulmonary veins and the right atrium.

Jarisch and associates[1] working on the cat noted that after severance of these nerves faradic stimulation of the vagus nerve in the neck failed to influence the heart beat. No recordings were made in these experiments but we feel that our work confirms and amplifies the results of these authors.

However, the theory of "denervation" cannot satisfactorily explain our results since it does not explain the reappearance of vagus inhibition when a further clamp is applied; thus, if the atrial escape is due to blocking of vagal fibers going to the sinus node, and thereby preventing local release of acetylcholine, we cannot explain how an additional clamp permits vagal effects to reappear.

In 6 experiments some of the vagus pathways were interrupted by crushing or by the application of broad ligatures to the right of the sinus node and at the area of the muscle bundles which connect the head of the sinus node with the left atrium. The results were unchanged.

SUMMARY

Systematic application of clamps across the sinus node leads at first to progressive inhibition of vagal influence on the sinus node activity and then to restoration of this effect. The mechanisms of these paradoxical results are discussed but no satisfactory explanation is evident.

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THE TsÊ LOOP IN HYPERCHOLESTEROLEMIA

H. KARNI, M.D.*

STOCKHOLM, SWEDEN

SINCE recent advances in our knowledge of lipid metabolism have established a basis for successful preventive treatment of hypercholesterolemia and presenile atherosclerotic manifestations accompanying it, early diagnosis of this condition is of the utmost importance. As is known from numerous necropsies, atherosclerotic and arteriosclerotic changes in the coronary arterial system are frequently encountered without having produced any subjective symptoms of myocardial disease. Since it has been evident that vectorcardiography is a diagnostic aid yielding valuable additional information as to the date, extension, and sometimes even the nature of the myocardial injury, a vectorcardiographic study of 14 hypercholesterolemia cases has been undertaken according to the principles reported previously.[5]

METHODS

The apparatus and vectorcardiographic methods have been described earlier.[4,5]

In Cases 1 through 9, Table I, serum cholesterol was estimated by Bloor's[1] method. Normal limits for adults according to this method were 150 to 300 mg. per cent. In Cases 10 through 14, Pearson's[6] method was employed. Here, the normal level was considered to lie between 170 and 240 mg. per cent.

Blood samples for serum cholesterol estimation were taken when the stomach was empty.

MATERIAL

The series consisted of 14 hypercholesterolemia cases. Nine were from the Medical Department of the University Hospital of Gothenburg (Cases 1-9, Table I); the remaining 5 were from the Contagious Diseases Hospital, Stockholm.

There were 6 women and 8 men in the series. The average age in the former group was 51 years, and that in the latter group, 50 years. In 9 patients there was a striking history of early arteriosclerotic manifestations or of sudden heart death in the family. In 2 other patients the information as to heredity was so vague that only uncertain conclusions could be drawn as to the occurrence of presenile arteriosclerotic manifestations in the family. In 3 cases a positive history could be excluded. Eleven patients suffered from moderate or severe anginal pains on physical or psychic stress. Furthermore, in 3 angina pectoris patients (Cases 3, 5, and 10) coronary artery occlusions could have been previously verified clinically. In 11 cases there were xanthomatous infiltrations of eyelids or tendons. The average serum cholesterol level was markedly elevated, although 10 of the patients were on restricted diets. In the women patients it was 440 mg. per cent; in men, 415 mg. per cent. Dietary restrictions consisted of limitation or exclusion of cholesterol-rich foodstuffs, such as animal fat, etc. Moreover, Cases 2, 11, and 14 were treated with heparin.

*Present address: Astrakang, 4, Stockholm-Vallingby, Sweden.

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TABLE I. RESULTS OF ECG AND VCG EXAMINATIONS IN 14 CASES OF HYPERCHOLESTEROLEMIA

CASE	SEX	AGE (YEARS)	HEREDITARY	ANGINAL PAINS	XANTHOMATOUS INFILTRATIONS	SERUM CHOLESTEROL MG. %	DIETARY RESTRICTIONS	ECG	VCG
1	♀	62	−	++	+	338	+	Slight (1 mm.) depression of S-T interval in leads corresponding to the left ventricle	Potential of injury and disintegration of the resultant T vector. Anoxic damage to the left ventricle
2	♀	51	++	−	++	580	+	Normal	∧dA 150°. Disintegration of the resultant T vector. Changes in the left ventricle
3	♂	63	?	++	++	350	+	Normal	Damage to the left ventricle
4	♀	38	+++	++	++	400	+	Slight depression of S-T interval in leads corresponding to the left ventricle	Anoxic area in the left ventricle
5	♂	53	+++	++	++	500	+	Pathologic T waves in certain leads	Old changes corresponding to the left ventricle
6	♀	63	++	+	−	500	+	Normal	Disintegration of the resultant T vector. Anoxic damage in the left ventricular wall

7	♂	49	++	++	++	456	+	Depression of S-T in Leads I, II. CR_5, and CR_7; T negative in I, CR_7. Acute myocardial damage?	∧dA 150°. Potential of injury. Old changes in the left ventricle
8	♂	48	?	±	+	278	+	Normal	Normal
9	♀	40	+	−	+	329	−	Normal	Normal
10	♂	48	+++	++	++	400	−	Acute myocardial infarction	Acute myocardial injury
11	♀	52	+	++	++	384	+	Increased duration of QRS. Coronary insufficiency corresponding to the left ventricle	Sudden changes in the pathway of depolarization
12	♂	50	−	++	−	608		Normal. Hypoxemia test clearly positive 1955, but negative 1956	Potential of injury during hypoxemia test, 1956
13	♂	48	+	++	+	324	+	Depression of S-T in Leads I, CR_5, and CR_4	∧dA 150°. Potential of injury corresponding to the left ventricle. Old and acute changes
14	♂	40	−	−	−	406	−	Normal	Normal

Following, a typical case is reported in order to exemplify the course of the illness and to illustrate the contrast between the ECG and the VCG findings.

CASE REPORT

Case report* of an engineer, aged 63 years (Case 3, Table I). Since 1943, his blood pressure had shown moderate elevation (210/110 mm. Hg). In recent years he had suffered from increasing anginal pains during rapid walking and effort of other kinds. These symptoms became worse and he could walk only 200 to 300 M. before precordial, radiating pain halted him. In 1954, this anginal pain intermittently disabled the patient. However, the ECG, which was checked several times, did not show any definite pathologic changes. In 1952, a moderately elevated serum cholesterol level was established and xanthomatous plaques could be observed on the eyelids.

On Oct. 19, 1955, he was admitted again to the Medical Department because of constant precordial pain. Though no myocardial infarction could be verified by means of ECG tracings, the clinical picture suggested such a process. After this episode the blood pressure showed a fall to 160/95 mm. Hg. Serum cholesterol was now 300 mg. per cent. Besides xanthomatous plaques on the eyelids, some infiltrations were found in certain tendons. Chest x-ray revealed enlargement of the left ventricle. The heart volume was approximately 500 c.c./M.^{2} of body surface.

The VCG, when analyzed with respect to changes in the TsÊ loop, showed pathologic features as to the formation of the integration vector of the repolarization phase, as well as the occurrence of the residual potential after the depolarization phase. There was, after depolarization, a residual charge, the potential of injury, preventing the QRSsÊ loop from returning to the zero point (Fig. 1). Pathologic changes could be seen only in the sagittal and horizontal plane projections. The TsÊ loop of the frontal plane projection seemed to be normal. However, this is a delusive projection that conceals the real features of the TsÊ loop, which is almost perpendicular to this plane. The disappearance of the predominant long axis of the TsÊ loop showed that a disturbance of the vectorial balance was present. This had been caused by T-vector components, which normally are not manifest. The potential of injury vector seemed to point backward, downward and to the left (line a-b).

The potential of injury is believed to indicate the existence of an ischemic zone in the myocardium, while the disturbance in the integration of instantaneous T vectors, called T-vector disintegration, is caused by necrosed myocardial fibers. The disintegration of the instantaneous T vector is due to the damage to a number of myocardial fibers, resulting in total loss of their membrane activity, whereas the potential of injury indicates, it is believed, a disturbance in charge activity of anoxic myocardial membranes.[5] Three subsequent VCG examinations at intervals of 1 week did not show any change in the vector loops. Electrocardiographic tracings remained normal.

Thus, the present vectorcardiographic diagnosis lends weight to the clinical diagnosis of myocardial infarction and makes the subjective symptoms more understandable.

RESULTS

A. *Cases With Normal ECG Recordings.*—Perhaps the most interesting result of this study is the high incidence of normal ECG findings (7 cases), though apparently inconsistent with both the history and certain objective findings. In 3 of these 7 cases there were moderate or severe anginal pains of effort type. In a fourth patient the pains were only vague. One patient had been treated for a clinically typical myocardial infarction (Case 3; see case report above). In 3 patients with normal ECG's xanthomatous infiltrations were absent. In all but 1 patient in this group the serum cholesterol level was elevated. When this investigation was performed, it was near the upper limit, but repeated analyses earlier had shown constant elevation. It is significant that the incidence of

*From the Medical Department I, University Hospital of Gothenburg; No. 856/52.

symptoms and signs of myocardial disease or sudden heart death in the families of the patients with normal ECG findings showed no exception in this respect from other patients in the series. In 2 patients of this group there was no family history of presenile vascular disease (Cases 12 and 14). However, the first case was not believed to represent a primary form of hypercholesterolemia. The disturbance of the actual lipid metabolism was considered to be caused by hypothyreosis (basal metabolic rate −27 per cent). Case 14, too, represented a somewhat obscure clinical picture. Here the pains were localized in the abdomen. Serum cholesterol, however, was constantly elevated. A possibility of vascular damage in the abdominal region could not be ruled out.

In 4 of the cases with negative ECG findings, definitely pathologic features were observed in the VCG.

Case 2, Table I, showed a deviation angle (dA) of approximately 150° between the long axes of the QRSsÊ and TsÊ loops. Moreover, there was an increase in width of the TsÊ loop. This patient showed a negative ECG reaction in the exercise test. During hospitalization, when she was treated with a diet poor in fat and with heparin, VCG changes towards normality were established. The dA diminished in 7 days to approximately 90°. It was within normal limits when examined again 1 week later. Simultaneously, there was a decrease in the disintegration of the T vector, causing a narrowing of the TsÊ loop. As will be seen from Table I, this patient had never suffered from any symptoms of myocardial disease. Nevertheless, it was here a question of primary hypercholesterolemia with a family history.

Case 3 has been described in detail in the case report above. The results of the VCG examinations were consistent with the clinical symptoms of organic myocardial disease. Repeated ECG tracings (standard and unipolar extremity leads and precordial Leads CR_3 through CR_7) were not informative.

A third case with unexpectedly normal ECG tracings, but with clearly pathologic features in the VCG, was Case 12. This patient showed a positive VCG reaction in the hypoxemia test. During inhalation of 10 per cent oxygen mixture, there was, from the eighth minute until 2 minutes after the test, an increasing potential of injury in the TsÊ loop. Simultaneously recorded ECG's, including standard and unipolar extremity leads and precordial leads from CR_1 through CR_7, did not show any depression of the S-T interval or any other pathologic signs.

In Case 6 there was no predominating long axis in the TsÊ loop; it was almost circular. In addition, a potential of injury was observable, leaving the loop open between zero point and the point where depolarization finished. The ECG's (I, II, III, CR_1 through CR_7) were normal. The blood pressure was 235/120 mm. Hg. Chest x-rays showed normal configuration and volume of the heart.

B. *Cases With Slight ECG Changes.*—In Case 1 there was only a slight depression of the S-T interval in Leads I and II and in the precordial Lead CR_{IV}. Sagittal and horizontal plane projections of the VCG revealed a rather marked potential of injury, the vector of which was almost vertical (Fig. 2).

Case 4 represents almost similar conditions with respect to the configuration of the TsÊ loop. There was, however, an even more marked potential of

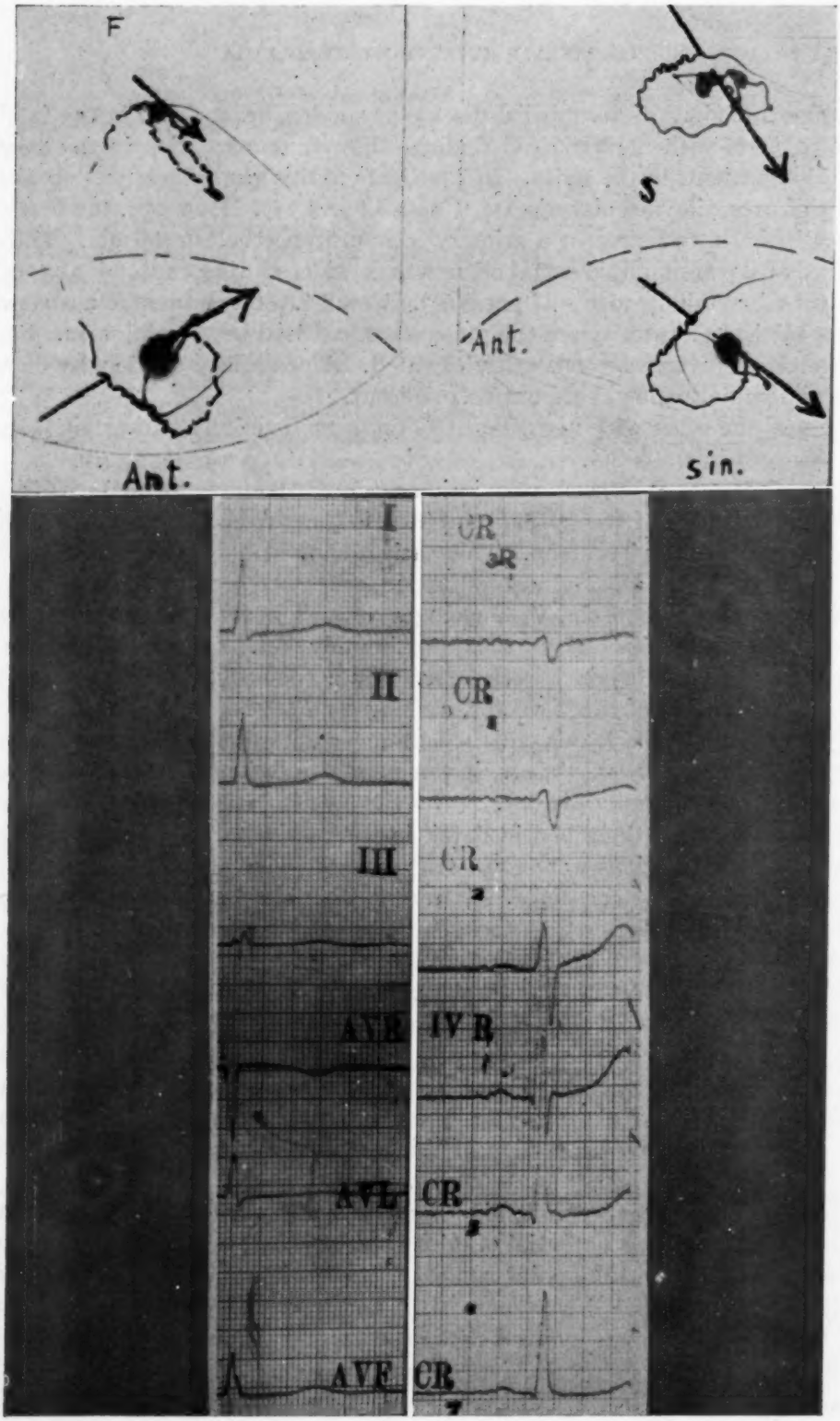

Fig. 1.—Frontal (*F*), horizontal (*H*), and sagittal (*S*) plane projections (top) in Case 3. The *F* plane projection is apparently normal. From the *S* and *H* plane projections will be seen the residual potential difference, which prevents the afferent limb of the QRSsÊ loop from returning to zero. There is also no predominant long axis of the TsÊ loop. The PsÊ loop is clearly visible from the *S* and *H* plane projections. The QRSsÊ loop is only partially visible. Amplification: 1 mv. = 9 cm. on the screen. The ECG, which was checked repeatedly, was normal (bottom).

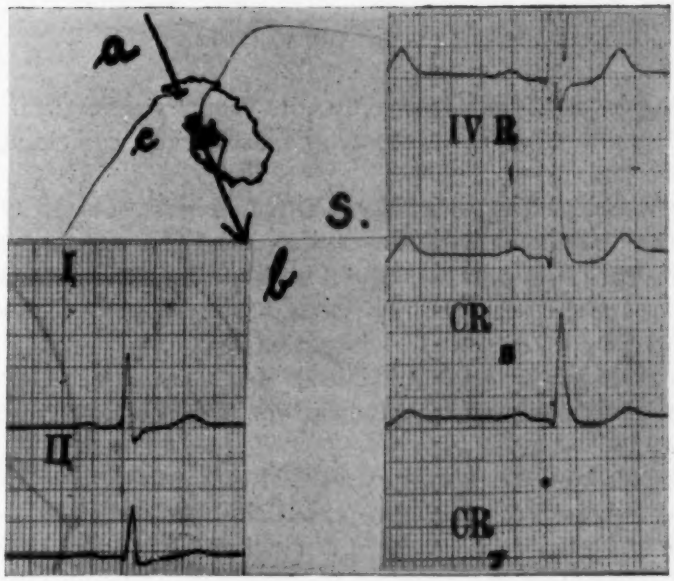

Fig. 2.—The TsÊ loop of the sagittal plane projection in Case 1, seen from the right side, and some selected ECG leads with only slight depression of the S-T interval. Maximal depression of S-T in Leads II and IV R (apex). The failure of the linear ECG registration to record sufficiently the existing potential of injury is attributed to the almost vertical position of its vector (*a-b*), causing only small projections on the ECG lead axes. There is also a pathologic displacement of phase between the T waves of different ECG components. It is so slight, however, that only the VCG recording makes it manifest. It can be seen from the increased width of the TsÊ loop which is nearly ellipsis-shaped.

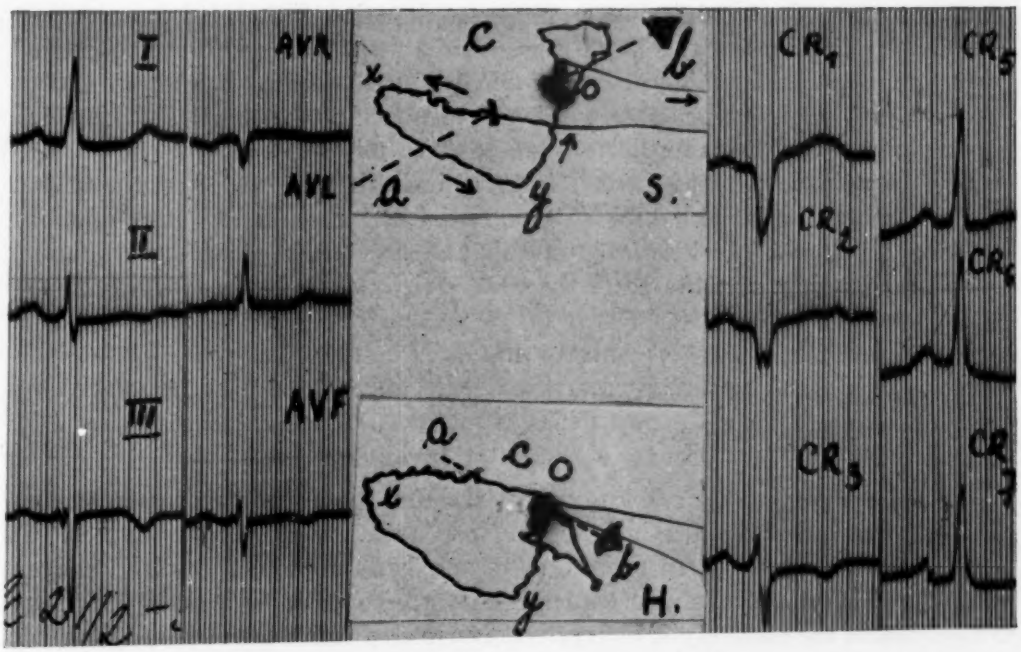

Fig. 3.—Showing the sagittal (*S*) and horizontal (*H*) plane projections of the PsÊ and TsÊ loops in Case D. D., and the effect of the less vertical vector of the potential of injury upon the ECG leads. In the sagittal plane projection this vector (*a-b*) is seen from the left side; in the horizontal plane projection, from above. It is directed posteriorly, cranially, and, as can be seen from the horizontal plane projection, somewhat to the left. The TsÊ loop is broad and slightly triangular. Its resultant vector first moves anteriorly, then turns abruptly to the left and posteriorly (*x*), and finally curves steeply upward (*y*) reaching zero (*0*). *C* = potent'al of injury. Small arrows indicate the direction of rotation of the QRSsÊ and TsÊ loops.

injury measuring 0.3 mv. In this case, too, its vector was vertical. In the ECG there were only minimal signs of coronary insufficiency, coinciding with the left ventricle.

C. *Cases With Strikingly Pathologic ECG Changes.*—The ECG's from Cases 5 and 7 were more consistent with the pathologic VCG projections and the clinical picture. In Case 5, the VCG showed an abnormally increased dA between the long axes of the QRSsÊ and TsÊ loops. The shape of the TsÊ loop was totally dominated by its long axis. No potential of injury was observable. In Case 7 there was, in addition to an increased dA, a potential of injury which left the TsÊ loop slightly open. The TsÊ loop was spindle-shaped and its long axis predominated.

Case 10 represented an acute myocardial infarction. The ECG showed a deep Q wave and signs of demarcation potential in precordial Leads CR_{2-3}. The TsÊ loop showed anterior displacement. Angle dA was about 90° at the first examination 2 days after the onset of the acute infarction. It decreased very slowly during healing of the process. The shape of the TsÊ loop was circular, due to disintegration of the T vector. There was a small potential of injury at the first examination. It disappeared, however, in a few days. Two weeks after the onset of the acute episode the TsÊ loop was narrow and its long axis increasingly distinct.

In Case 11 the ECG showed not only signs of coronary insufficiency corresponding to the left ventricle, but an increased duration of the QRS complex. In all 3 plane projections of the VCG there were abrupt changes in the succession wave of depolarization which made the QRSsÊ loop uneven. It was triangular, with an acute angle pointing forward and somewhat to the left. The ECG changes had been more marked 1 year before these investigations were performed, showing deep depressions of the S-T interval in leads from the left precordium.

In Case 13 the VCG exhibited a potential of injury in the TsÊ loop and discordance between the long axes of this and the QRSsÊ loop corresponding to the left ventricle. In the ECG there were signs of coronary insufficiency.

DISCUSSION

In the present study, attention was given chiefly to the characteristics in the changes of the TsÊ loop. In this respect the evaluation was based on 2 main points:

1. The presence of a residual potential difference in the heart muscle after the depolarization phase, leaving the TsÊ loop open. Such a disturbance in the electrical activity is believed to be due to anoxic damage to the membranes of the myocardial fibers. Damaged membranes are thought to possess their own rhythmicity in the electrolytic charge. This causes a residual potential difference between anoxic and intact parts of the myocardium. Brofman and associates[2] showed experimentally that a local anoxic state was responsible for a potential difference between this and the remaining normal part of the heart muscle. When the anoxemia was spread diffusively throughout the entire heart muscle, no potential difference could be established, corresponding to the electrically balanced conditions in the normal myocardium.

2. The disintegration of the resultant T vector due to loss of a number of myocardial fibers from the integration of the instantaneous vector. This phenomenon has been described in detail previously.

It is beyond doubt that the displacement of the phase between the ECG components, which causes loss of the predominating long axis of the TsÊ loop in myocardial injury, is also responsible for the more distinct potential of injury in the VCG than its counterpart in the ECG: depression of the S-T interval. In point of fact, this depression represents only a projection of the potential of the injury vector. If this vector is increasingly vertical, its projection on the lead axis will decrease progressively. Hence, the ECG tracing shows only a relative amount of the potential of injury, whereas the VCG projections enable its degree to be evaluated more indirectly and, therefore, with greater accuracy. From the potential of injury in the 3 perpendicular plane projections, an approximate idea can be gained of the absolute voltage of the residual potential difference. Furthermore, these 3 plane projections convey some idea of the stereometric localization of the vector in question. Fig. 2 illustrates the effect of the almost vertically localized vector of the potential of injury upon the ECG leads. The potential of injury points almost caudally. Fig. 3 shows some ECG leads and some sagittal and horizontal plane projections from a case in which the potential of injury vector was less vertical. These recordings were made from a 58-year-old man (Case D.D.) suffering from severe anginal pain for 2 months. Arrow *a-b* indicates the potential of injury vector. It points towards the zero point posteriorly and cranially. The anterior wall of the left ventricle was thought to have a large anoxic area, presumably a sign of incipient infarction. A month after these recordings were made the patient suddenly fell ill. The anginal pain, formerly occurring only on effort, was now continuous. The sedimentation rate increased from 17 mm., one week before the acute onset, to 105 mm. On the second day of the sudden illness the patient died. Necropsy revealed old and fresh myocardial changes in the anterior wall of the left ventricle, which was aneurysmatic. The process involved the anterior part of the septal wall, too. In the posterior wall there were old scars only (Pathologic Department, St. Görans Sjukhus, Stockholm; Case 130/56).

In Cases 1 and 4 there was a vertically located potential of injury vector. This explains the minimal depression of the S-T interval in both cases, although the absolute voltage of the residual potential difference caused by the anoxemia was apparently much greater. The grave subjective symptoms in these cases, and especially those in Case 4 with a family history of sudden heart death in 2 brothers and 1 sister, are, with the vectorial interpretation, more understandable.

In Cases 1, 2, 3, and 6 the disintegration of the resultant T vector caused an increase in the width of the TsÊ loop. In Cases 1, 3, and 6 this phenomenon appeared together with a potential of injury. Though there were very marked changes in the VCG, repeated ECG tracings were quite normal or showed only minimal changes, as in Case 1. The displacement of phase in 2 simultaneously recorded perpendicular ECG leads (V_1-aV_F, I-aV_F and I-V_1) explains the sensitivity with which disturbances of electrical forces can be recorded by means of VCG-plane projections. As regards Case 2, a VCG follow-up showed a ten-

dency to normalization, while no ECG changes were detectable during the observation time. Although the patient had no subjective symptoms of myocardial disease, VCG findings can hardly be ignored, bearing in mind the high incidence of myocardial disease of vascular origin in hypercholesterolemia, especially in cases with a positive heredity. In a case like this, in which subjective symptoms were absent but in which experience and several investigations suggested that myocardial disease was highly probable, VCG examination is of great importance. VCG results pointing to myocardial disease in cases with only slight ECG changes, or none at all, but representing clinically a well-defined group with anginal pain and family histories of sudden heart death or myocardial disease at early ages, strengthen the conviction that VCG examination may, in many cases of heart muscle disease, yield additional information facilitating evaluation of the clinical picture and subjective symptoms.

No less important is the VCG diagnosis in cases with histories of multiple myocardial infarctions. Here, especially, the shape of the TsÊ loop may provide valuable information as to the age of the myocardial injury. In Cases 5 and 7 it was possible by means of the VCG diagnosis to exclude an acute myocardial injury. However, the almost total discordance of the long axis of the QRSsÊ and TsÊ loops pointed to old myocardial lesions. In Case 3 the VCG signs suggested the possibility of an acute infarction shortly before, although the conventional ECG curves over a longer observation period were negative.

In Case 11 the VCG change concerned mainly the QRSsÊ loop. It revealed a sudden change in the direction of the succession wave during depolarization. This phenomenon has been encountered in dogs with thallium-induced myocarditis.[4] Young and associates[3,7] have reported similar unevenness in the pathway of the QRSsÊ loop in myocardial infarction.

In Case 12, with completely normal ECG tracings at rest and during the hypoxemia test at the last examination, the patient complained of severe intermittent angina pectoris. The ECG had been clearly pathologic for a couple of months before the present investigation was carried out, showing depression of the S-T interval in leads corresponding to the left ventricle. Actually, an increasing potential of injury was observable in the sagittal plane projection of the VCG recorded during the hypoxemia test. ECG controls were taken simultaneously. This patient showed partial paresis of the right hand. A causal relationship between this symptom and the high serum cholesterol level (608 mg. per cent) was suggested. A vascular cerebral angiopathy was considered probable. These circumstances lend weight to the notion of a more general vascular disease involving the myocardium. VCG diagnosis of an anoxic state in the myocardium when the ECG is negative indicates the great value of the method in recording of heart muscle potentials.

The VCG results in this series warrant the employment of this method in the examination of patients with a number of subjective cardiac symptoms but few, if any, objective findings, clinically grouped as an entity: heart neurosis. Many clinicians may have gained the impression that the incidence of myocardial infarction in higher age groups in this series was greater than in patients with no history of subjective cardiac symptoms.

CONCLUSIONS AND SUMMARY

1. In 7 of the 14 hypercholesterolemia cases in the present series there were both ECG and VCG indications of myocardial disease.

2. Two of these 7 cases with VCG signs of advanced myocardial disease presented only minor changes in the ECG, although the clinical signs and subjective symptoms, the severity of anginal pain, and the duration of the illness suggested grave myocardial disease. One of these patients had a striking family history of myocardial disease and sudden heart death.

3. In 4 patients, 3 of whom suffered from severe anginal pain and were clinically assigned to a group with advanced myocardial disease, the ECG's were negative, whereas the VCG's showed pathologic features. One of these patients had been admitted to the medical department shortly before this investigation, owing to a clinically manifest myocardial infarction. Repeated VCG recordings showed old and acute myocardial lesions.

4. It is shown that VCG signs in the diagnosis of myocardial conditions are sometimes more closely correlated to the clinical picture than are the ECG tracings.

5. Two circumstances are believed to make the VCG recording more sensitive: (a) The displacement in phase, which, causing loss of the distinct long axis of the TsÊ loop and increasing the width of this loop, is responsible for the disintegration of the resultant T vector. (b) The more direct registration of the potential of injury by means of VCG. The depression of the S-T interval, which represents its ECG counterpart, is only a projection of the potential of injury vector on the lead axis in question. When the potential of injury vector is perpendicular, its projection on ECG leads is zero.

6. VCG examination is recommended in cases with subjective cardiac symptoms where only meager objective symptoms or none at all are present.

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ATRIAL FIBRILLATION IN SYPHILITIC AORTIC INSUFFICIENCY

A. B. SMITH, M.D., AND THOMAS N. STERN, M.D.

MEMPHIS, TENN.

THE statement that atrial fibrillation is rarely found in association with syphilitic heart disease may be found in any current medical or cardiology text. Thus, Stewart in Cecil and Loeb's *Textbook of Medicine*[1] states that fibrillation is associated infrequently with syphilitic forms of heart disease; White[2] makes the statement that atrial fibrillation is uncommon with cardiovascular syphilis; and Prinzmetal[3] in his monograph on the auricular arrhythmias says that syphilitic heart disease seldom is associated with atrial fibrillation. Relying on these statements we frequently found ourselves in diagnostic error, disregarding syphilis which was later found to be present. In an effort to determine the actual incidence of atrial fibrillation in syphilis, we reviewed the records of the John Gaston Hospital.

During the period 1950 to 1954, there were 13,100 original admissions to the medical service of the hospital. Of this group the primary diagnosis of rheumatic heart disease was made in 279 patients. Atrial fibrillation was present on electrocardiogram in 42, or 14.3 per cent, of these. The diagnosis of syphilitic aortic insufficiency was made 125 times during the same period and of these patients 14, or 11.2 per cent, were found to have atrial fibrillation. In all cases the diagnosis was made on the basis of classical aortic insufficiency, a positive serologic test for syphilis and/or a history of syphilis, and the absence of history or findings of other disease that might cause aortic insufficiency. The only exceptions were those cases proved at post-mortem to be syphilitic. For the purpose of this series atrial fibrillation was not considered to be present unless proved by ECG. Three typical case histories will be presented.

Case No. 1, #225429.—H. M., a 48-year-old Negro man, was seen first in the Outpatient Department on Sept. 17, 1953, with symptoms and signs of cardiac insufficiency. The onset of symptoms was in 1950. They had progressed through exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ankle edema, frequency, nocturia, and abdominal distention. There was a history of gonorrhea 18 years previously and treatment for syphilis in 1950. Physical examination revealed a 6-foot, 142 pound man in no acute distress. There was neck vein distention. There were fine moist inspiratory râles in both lung bases. The heart was enlarged, with the point of maximal impulse in the seventh left intercostal space in the anterior axillary line. No thrill was palpable. There was a loud blowing Grade 3 decrescendo, aortic diastolic murmur, and a high-pitched Grade 2 aortic systolic murmur. An Austin-Flint murmur was thought to be present. The blood pressure was 196/50 mm. Hg and the pulse was totally irregular. A water-hammer pulse was palpable and a Duroziez sign was elicited. The liver was not enlarged and no evidence of ascites or edema was found. Three months later, however, when he was admitted to the hos-

From the Department of Medicine, University of Tennessee College of Medicine, and the John Gaston Hospital, Memphis, Tenn.

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pital in full-blown heart failure, there was ascites and the liver was palpable 4 fingerbreadths below the right costal margin. The serologic test for syphilis was positive to 32 dilutions. The electrocardiogram showed atrial fibrillation and also left ventricular hypertrophy, which was confirmed by x-ray. He was digitalized and treated with mercurial diuretics and discharged home well compensated.

Case No. 2, #125171.—F. S., a 58-year-old Negro man, was admitted to the John Gaston Hospital in 1947, with symptoms but no signs of cardiac insufficiency. There was no history of rheumatic fever, but he had gonorrhea in 1927. He had a Grade 3 diastolic and a Grade 2 systolic murmur heard best over the aortic area. A systolic and diastolic thrill were present over the aortic area. A Corrigan pulse and Duroziez sign were demonstrable. The blood pressure was 170/66 mm. Hg. At this time his cardiac rhythm was regular at 84 beats per minute. He was diagnosed as having syphilitic aortitis, aortic insufficiency, and myocardial decompensation. He became asymptomatic on bed rest and a low-salt diet. Seven negative Kahn tests were obtained between the years 1947 and 1951, with no positives occurring. He was admitted to the hospital again in July, 1951, with signs and symptoms of cardiac insufficiency. Once more the peripheral and central signs of aortic insufficiency were found. He now had atrial fibrillation and because of this the diagnosis of syphilitic heart disease was questioned. Intensive therapy failed to revert the cardiac insufficiency, and he died.

Autopsy: At autopsy (A-51-565) the heart weighed 910 grams and was massively dilated. The aortic valve circumference was 10 cm. There was thickening of the aortic valve characteristic of syphilis but no definite fusion or separation of the cusps. The mitral valve ring circumference was 13 cm. and the valve leaflets revealed no significant alterations. Grossly, the ascending aorta showed the classical tree-barking effect; microscopically, it showed medial degeneration and scarring, infiltration with lymphocytes, adventitial thickening, and thickening of the vasa vasorum.

Case No. 3, #110473.—T. M., a 72-year-old Negro man, was admitted to the John Gaston Hospital Dec. 3, 1951, for the twelfth and last time since 1948. There was a history of a penile lesion in 1928, with partial therapy for syphilis at that time. In 1949, a serologic test for syphilis showed 10 Kahn units. On each admission the patient had signs and symptoms of cardiac insufficiency. He was found repeatedly to have cardiomegaly with predominantly left ventricular enlargement. A precordial to-and-fro murmur was described, the diastolic component being decrescendo, replacing the second heart sound and loudest just to left of sternum in the fifth intercostal space. The systolic component was rather coarse and was loudest over the primary aortic area. A Corrigan pulse, Duroziez sign, and "pistol shot" sound over the femoral artery were described on these admissions. On most admissions the cardiac rhythm was reported as being irregular, but not until this last admission was an electrocardiogram obtained which showed atrial fibrillation. He died in intractable cardiac failure.

Autopsy: At autopsy (A51-864) the heart weighed 720 grams. The aortic valve ring circumference measured only 8 cm. but there was "rolling of the edges of the valve cusps with separation of the cusps," and the valve was demonstrated to be incompetent. Throughout the aortic valve leaflets there was round cell perivascular infiltration. Toward the base of the leaflets there was a fair amount of elastic tissue and moderate cellularity. Toward the tip there was a rather abrupt change from the previously described tissue to a dense, hyalinized fibrous tissue with very scant cellularity. The mitral valve ring circumference measured 12 cm. and the leaflets showed no significant changes. The aorta presented both a gross and microscopic picture of syphilitic involvement. There were numerous small areas of scarring in the media surrounded by round cells. "The adventitia is thickened and fibrosed and in some areas is actually thicker than the media. There is an obliterating endarteritis and perivascular cuffing of the vasa vasorum. The adventitia is also sprinkled with round cells, some of which are seen as small islands. The intima is thickened and fibrosed and there is evidence of calcification."

DISCUSSION

The prevalent concept that atrial fibrillation and syphilis are infrequently associated would appear to derive from various studies of atrial fibrillation in which syphilis was unimportant on a percentage basis as an underlying cause of

fibrillation. This conclusion obviously does not depend solely on the relationship of syphilis and fibrillation but would vary with the number of cases of syphilis as compared to those of other types of heart disease. Evans[4] found that syphilis was present in 1.5 per cent of 2,958 cases of established atrial fibrillation; the figures of Parkinson and Campbell[5] were 2.5 per cent. In neither of these papers, however, is the reverse considered, that is, the incidence of fibrillation in syphilitic heart disease. This question was considered by Plice and Pfister[6] who found that 45 out of 244 syphilitic patients had atrial fibrillation. This incidence of 18.4 per cent compares well with our findings of 11.2 per cent. These values assume even more significance when compared to 14.3 per cent, the incidence of fibrillation in rheumatic heart disease at our hospital, and 12.5 per cent, the incidence of fibrillation in an unclassified group of 3,000 cardiac patients studied by White and Jones.[7]

Why do atria fibrillate? It is generally agreed[3,8] that the principal factor in producing fibrillation is the stretching or distention of the atria as the result of increased intra-atrial pressure. Vagal stimulation is believed to play an as yet undetermined role in producing this arrhythmia.[9] There are no demonstrable pathologic changes to explain the phenomenon.

The most common cause of increased atrial pressure is left ventricular failure, regardless of the etiology of the heart disease. The second most common cause of increase in atrial pressure is mitral stenosis. In mitral stenosis the atrial distention and intra-atrial pressure increase necessary to precipitate atrial fibrillation may occur well before clinical "heart failure." As a result of this fact atrial fibrillation occurs earlier in cases with rheumatic heart disease than in cases with syphilitic heart disease.

We are unable to find any anatomic, pathologic, physiologic, or philosophic reason for atrial fibrillation being "rarely" associated with syphilitic heart disease. Our statistics, as well as those of others, indicate that the incidence is relatively high. There may be a socioeconomic explanation however. It well may be that the incidence of syphilitic heart disease seen late and untreated is low except in large charity centers. This, however, should not justify the perpetuation of inaccurate conclusions. In our location, atrial fibrillation occurs statistically as often in syphilitic heart disease as it does in rheumatic heart disease. It is our opinion that atrial fibrillation should not be used as a differentiating point between rheumatic heart disease and syphilitic heart disease, except possibly in patients who have never shown signs or symptoms of cardiac insufficiency.

SUMMARY

Atrial fibrillation has been found to be present in 11.2 per cent of all cases of syphilitic aortic insufficiency at the John Gaston Hospital. This percentage compares roughly with the incidence in rheumatic fever (14.3 per cent) at our hospital, and the overall incidence of fibrillation in a large series[7] of unselected cardiac cases (12.5 per cent). It is concluded that presence or absence of fibrillation cannot be used as a differential diagnostic point between syphilitic and rheumatic aortic regurgitation.

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DIAMOX (ACETAZOLEAMIDE) AS AN ORAL DIURETIC IN AMBULATORY CARDIAC PATIENTS

WARREN S. BRAVEMAN, M.D.* RICHARD L. DEXTER, M.D.**
AND ALBERT L. RUBIN, M.D.***

NEW YORK, N. Y.

SINCE the introduction of parenteral mercurial diuretics, there has been a continuous search for an effective orally administered diuretic agent. Two types—organomercurial compounds and the carbonic anhydrase inhibitor, Diamox (acetazoleamide)—are now available. The oral mercury compounds usually require administration of several pills in divided doses each day for achievement of the desired diuretic effect. Their use has been associated with gastrointestinal symptoms and gingival reactions.[1-3] Further practical advantage would accrue to an oral agent effective in a single daily dose. In our experience, Diamox (2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide) not only fulfills this criterion, but also has proved to be safe and free of disturbing side effects in the dosage used.

MATERIAL AND METHODS

Twenty-one ambulatory patients with edema secondary to congestive heart failure who regularly attend the Second (Cornell) Medical Division Cardiac Clinic at Bellevue Hospital were chosen for this study. Their clinical status is summarized in Table I. Their ages ranged between 38 and 84 years, and averaged 64 years. Ten of the group had underlying arteriosclerotic heart disease, 4 had hypertensive heart disease, and 4 had rheumatic heart disease. One each had syphilitic heart disease, cor pulmonale, and kyphoscoliotic heart disease. Functionally, by the criteria of the New York Heart Association, 9 patients were in Class II, and 12 were in Class III.

In every instance the patient had been adequately digitalized, and was on a regimen of maintenance digitalis and low-salt diet. Twenty of the 21 had been receiving 1 to 3 weekly injections of a mercurial diuretic for periods ranging from 6 months to 10 years (Table I). One subject (I. K.) with rheumatic heart disease was begun on Diamox therapy when he showed evidence of fluid retention for the first time.

From the Second (Cornell) Medical Division, Bellevue Hospital, and the Department of Medicine, Cornell University Medical College, New York City.

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*Instructor in Medicine, Cornell University Medical College; Assistant Clinical Visiting Physician, Bellevue Hospital.

**Assistant in Medicine, Cornell University Medical College.

***Assistant Professor of Medicine, Cornell University Medical College; Assistant Visiting Physician, Bellevue Hospital.

Patients were seen weekly during the first month of study, every 2 weeks for the next 2 months, and thereafter every 4 to 6 weeks. On each clinic visit, the patients were weighed, and blood samples drawn for determinations of plasma electrolyte concentrations (sodium, potassium, chloride, and carbon dioxide combining power). They were examined on each visit by one of two of us (W. B., R. D.) and questioned about subjective changes and possible side effects related to Diamox administration. Periodically, urinalyses, blood counts, and blood urea nitrogen determinations were carried out.

The only changes instituted in the treatment regimen was the substitution of Diamox—one 250 mg. tablet every other day—for parenteral mercurial diuretic therapy.

RESULTS

Diamox—one 250 mg. tablet every other day—maintained all of these ambulatory cardiac patients at optimal body weight as effectively as had parenteral mercurial agents. The average duration of therapy was 12.7 months, and 9 of the group were treated for 18 months. All except 2 (P. J., F. C.) who have since suffered fatal myocardial infarctions are still well maintained on Diamox therapy.

None of the minor side effects which can occur in the course of Diamox administration—paresthesias, anorexia, drowsiness—were reported by the patients at any time during the course of the study. This result appears to be directly related to the treatment regimen since, in the literature, undesirable effects usually have been associated with larger amounts of Diamox administered in divided daily doses.[4-6]

Serial studies of plasma electrolyte concentrations revealed no significant alterations in plasma electrolyte pattern at any time during the study. As can be seen in Table II, which tabulates the plasma concentrations of sodium, potassium, chloride, and bicarbonate ions, the only alteration was the development of a moderate hyperchloremia, the mechanism of which has been studied.[7]

Generally, the patients' average weights were lower while on Diamox therapy than they were during parenteral mercurial therapy (Table I). This should not be interpreted as reflecting greater potency as a diuretic agent for Diamox. While on mercurial therapy, prior to transfer to the Diamox regimen, the patients were weighed on each clinic visit prior to the administration of one of their weekly mercurial injections. However, the treatment regimen using Diamox was noted to result in less fluctuation in body weight, probably due to the shorter interval between doses, which allowed less time for fluid accumulation.

Table III charts the weight gain in 4 subjects who were observed for a short period of time without benefit of any specific diuretic administration. In patient W. B., this occurred by chance rather than direction. In each instance, the patient gained weight, and responded to reinstitution of Diamox therapy with a return to the edema-free state within 7 to 10 days.

The morale of all the patients improved considerably with substitution of Diamox for parenteral diuretic therapy in their treatment regimens. They were generally more comfortable, and sincerely appreciated the reduction in the number of visits to the Outpatient Department made possible by the elimination of the need for intramuscular mercurial injections.

TABLE I. CLINICAL AND THERAPEUTIC DATA ON 21 PATIENTS IN WHOM DIAMOX WAS SUBSTITUTED FOR PARENTERAL MERCURIAL THERAPY

PATIENT	AGE, SEX	HEART DISEASE (N. Y. HEART ASSOCIATION CRITERIA)	ASSOCIATED DISEASE	MERCURIAL THERAPY			DIAMOX THERAPY		
				LENGTH OF TIME ADMINISTERED (YEARS)	DOSAGE SCHEDULE	WEIGHT RANGE (LBS.)	LENGTH OF TIME ADMINISTERED (MONTHS)	DOSAGE SCHEDULE	WEIGHT RANGE (LBS.)
P.J.	65 M	HCVD, EH, LVH, Auric. Fibrill., III C.	Pulmonary Emphysema	2½	2c.c. biw	172–175	18	(250 mg.) every other day	159–165
F.D.	66 F	ASHD, EH, NSR, III C.	Bronchial Asthma, Chr. lung disease	2½	2c.c. tiw	162–165	18	(250 mg.) every other day	161–167
W.B.	68 M	ASHD, EH, LVH, Angina II B.	Diabetes mellitus, Gen'l. Arteriosclerosis	10	2c.c. biw	190–200	18	(250 mg.) every other day	165–180
J.C.	54 M	RHD, EH, MI, MS, Auric. Fibrill., II-III C.		2	2c.c. biw	170–175	18	(250 mg.) every other day	165–170
R.E.	53 M	RHD, EH, MI, NSR, III C.		4	2c.c. biw	200	18	(250 mg.) every other day	194
D.N.	74 M	ASHD, Myo. Inf., NSR, Angina, III C.		1½	2c.c. o w	200	18	(250 mg.) every other day	188–195
D.C.	78 M	SHD, EH, AI, NSR, Angina III C.	Aneurysm of ascending aorta	2	2c.c. biw	150–158	18	(250 mg.) every other day	146
E.M.	56 F	ASHD, EH, Auric. Fibrill., Angina, II C.		10	2c.c. tiw	190–220	18	(250 mg.) every other day	176
L.M.	69 F	HCVD, ASHD, EH, NSR, Angina, II C.	Recurrent Thrombophlebitis	2	2c.c. biw	115–120	18	(250 mg.) every other day	100–105

J.A.	61 M	Cor Pulmonale, EH, NSR, III C.	Pulmonary Emphysema	3	2c.c. biw	155–172	16	(250 mg.) every other day	150–154
I.K.	40 M	RHD, EH, MS, MI, Auric. Fibrill., III C.	Hypertension, CVA- (2° to Embolism)	—	—	130	12	(250 mg.) every other day	120
A.W.	38 F	Kyphoscoliotic heart disease, NSR, II B.		1½	2c.c. o w	95	12	(250 mg.) every other day	87–92
J.K.	63 M	ASHD, EH, Myo. Inf. NSR, Angina, III C.	Parkinsonism	5	2c.c. tiw	170–200	12	(250 mg.) every other day	170
C.W.	64 M	ASHD, EH, Auric. Fibrill., Angina, II C.		3	2c.c. biw	135–145	10	(250 mg.) every other day	138
J.W.	72 M	ASHD, EH, NSR, III C.	Pulmonary Emphysema	3	2c.c. biw	180	9	(250 mg.) every other day	171
J.W.	65 M	ASHD, EH, NSR, II C.		4	2c.c. biw	185–195	9	(250 mg.) every other day	180
F.C.	77 F	ASHD, EH, Auric. Fibrill., Angina, III C.	Laennec's Cirrhosis	2	2c.c. biw	149	6	(250 mg.) every other day	145
A.S.	84 F	HCVD, ASHD, EH, Auric. Fibrill., Angina, III C.	Diabetes mellitus, Obesity, General Arteriosclerosis	7	2c.c. o w	150–156	6	(250 mg.) every other day	147–150
H.S.	82 F	RHD, EH, AS, AI, MI, Auric. Fibrill., II C.		7	2c.c. biw	100–105	6	(250 mg.) every other day	94
R.D.	59 F	HCVD, EH, NSR, II C.	Obesity	½	2c.c. biw	155–165	4	(250 mg.) every other day	144
H.B.	55 M	ASHD, Myo. Inf., NSR, Angina, II B.		½	2c.c. o w	120–125	3	(250 mg.) every other day	120

KEY TO ABBREVIATIONS:

HCVD = Hypertensive Cardiovascular Disease
ASHD = Arteriosclerotic Heart Disease
RHD = Rheumatic Heart Disease
SHD = Syphilitic Heart Disease
EH = Enlarged Heart
LVH = Left Ventricular Hypertrophy
NSR = Normal Sinus Rhythm
MS = Mitral Stenosis
MI = Mitral Insufficiency
AI = Aortic Insufficiency
AS = Aortic Stenosis
Auric. Fibrill. = Auricular Fibrillation
Chr. = Chronic
CVA = Cerebrovascular Accident
biw = biweekly
tiw = triweekly
ow = weekly

TABLE II. OBSERVATIONS ON PLASMA ELECTROLYTES BEFORE AND DURING DIAMOX THERAPY FOR PERIODS UP TO 12 MONTHS

PATIENT	PRE-DIAMOX				DIAMOX THERAPY															
					3 MONTHS				6 MONTHS				9 MONTHS				12 MONTHS			
	Na^+	K^+	CO_2^-	Cl^-	Na^+	K^+	CO_2^-	Cl^-	Na^+	K^+	CO_2^-	Cl^-	Na^+	K^+	CO_2^-	Cl^-	Na^+	K^+	CO_2^-	Cl^-
	MEQ./L.	MEQ./L.	μMol./L.	MEQ./L.	MEQ./L.	MEQ./L.	μMol./L.	MEQ./L.	MEQ./L.	MEQ./L.	μMol./L.	MEQ./L.	MEQ./L.	MEQ./L.	μMol./L.	MEQ./L.	MEQ./L.	MEQ./L.	μMol./L.	MEQ./L
J.P.	135	4.5	—	109	135.5	3.7	22.5	110	140	4.1	26.7	116	140	3.5	26.4	111.4	140	3.7	26.9	110.6
F.D.	142	4.9	—	107	135.5	4.8	26.8	107	138	4.8	24.5	109	140	4.7	28.3	110.4	143.5	5.3	28.8	109.2
W.B.	138	4.7	29.7	111.2	139	4.3	28.4	108.4	138	4.0	23.6	113.2	135	4.4	23.8	110	135	3.8	25.1	108
J.C.	136	4.1	27	108.5	139	5.2	23.9	110.8	139	4.0	24	112	135.5	4.1	20.5	115.2	141.5	4.3	25	114.4
R.E.	139	4.1	26	108	140.5	4.4	26.5	111.6	140.5	4.2	21.6	118.6	139	4.1	21.1	117.2	140	4.2	21.5	115.2
D.N.	140.5	4.1	26.2	109.8	140.5	4.2	23.7	108	135.5	3.8	22.9	109.4	136.5	4.0	24.2	109.4	138.5	4.1	25.4	113.4
D.C.	138	5.2	24.5	111.8	135.5	4.1	20	110.4	138	4.7	20.6	114.2	135	4.3	22.5	113	137.5	4.3	19.6	115.8
E.M.	137	4.3	26.6	110	135.5	4.4	23.9	111.2	135.5	4.4	23.3	112	—	—	—	—	143.5	4.6	24.9	118
L.M.	135.5	4.2	24.8	105.8	138	4.1	21.1	109.6	135.5	4.2	21.6	111.2	137.5	4.2	19.5	107.4	—	—	—	—
J.K.	133	3.7	22.5	104.8	139	4.2	27.6	112.4	140	3.9	24	115.2	—	—	—	—	—	—	—	—
F.C.	138	3.7	30.4	106.2	137	4.2	24.2	112.2	137	4.1	23.8	112.8	—	—	—	—	—	—	—	—
A.S.	134.5	5.0	26.9	102.2	135.5	4.9	24.3	100	135.5	4.4	22.5	111.2	—	—	—	—	—	—	—	—
H.S.	138	5.6	29.1	104	132	4.7	24.9	109	135.5	4.6	22.8	109.6	—	—	—	—	—	—	—	—
J.A.	138	5.4	27	105	134	4.1	17.9	110.2	135	4.2	20.4	107.6	137.5	4.3	24.5	106.6	—	—	—	—
A.W.	130.5	4.1	21.2	107.4	135.5	4.0	22.1	111.4	130.5	3.9	20	112								
H.B.	133	4.8	25.5	106.2	135.5	4.9	22.4	112												
J.K.	128	4.2	26.1	108	136.5	4.0	24	112	137.5	4.0	23.4	113								
C.W.	133	3.8	23.4	112.8	141.5	4.2	25	116.6												
R.D.	137	4.3	27.1	106.8	135.5	4.6	26.6	111.4												
J.W.	143	4.6	25	110	147	4.7	21.5	116												

TABLE III. WEIGHT CHANGE WITH CESSATION AND REINSTITUTION OF DIAMOX THERAPY IN 4 PATIENTS

PATIENT	AGE, SEX	AVERAGE WEIGHT MAINTAINED DURING DIAMOX ADMINISTRATION LBS.	NUMBER OF WEEKS DIURETIC THERAPY WITHHELD WKS.	WEIGHT CHANGE WHILE OFF DIURETIC THERAPY LBS.	WEIGHT CHANGE RESUMPTION DIURETIC THERAPY LBS.
P.J.	65 ♂	162	4	+4.5	—7
W.B.	68 ♂	169	6	+20	—23
D.N.	74 ♂	192	5	+6	—10
D.C.	78 ♂	146	3	+5	—5

DISCUSSION

It is of particular importance in using Diamox as a diuretic drug to understand the chemical alterations induced by its administration, the duration of these alterations, and their influence on drug effect. This bears emphasis because Diamox is used also in the management of a variety of other diseases, including epilepsy, glaucoma, and emphysema, in which diseases a dosage schedule is used that would not be effective in mobilizing edema fluid.

The pharmacology of Diamox has been extensively studied and reported by Maren and associates.[8,9] Its inhibition of carbonic anhydrase activity in renal tubular cells results in a decreased reabsorption of bicarbonate ions, which is responsible for its diuretic activity. Following the administration of a single dose of Diamox, plasma bicarbonate concentration and plasma pH fall, producing a mild and harmless metabolic acidosis. In order for second and subsequent challenges with Diamox to produce a renal response, sufficient time for recovery from the initial bicarbonate loss—i.e., restoration of acid-base balance—must be allowed. Subsequent doses of Diamox will elicit less or no diuretic response if administered without regard for this principle. In cardiac patients with fluid retention, it has been our experience that a minimum of 24 hours, and often 48 hours, is the interval required between doses of Diamox for adequate bicarbonate restoration. In this study, an interrupted dosage schedule of 250 mg. every other day has been used with good effect. The divided daily dose schedule used in the management of glaucoma and epilepsy will effect little or no diuresis after the first day, and has no place in the mobilization of edema fluid in cardiac patients.

It follows from the above that patients with low body bicarbonate stores (reflected by low plasma carbon dioxide combining powers)—secondary to renal disease or ammonium chloride administration—will respond poorly, if at all, to Diamox administration. By contrast, patients with cor pulmonale, who have higher than normal bicarbonate levels, often respond to Diamox administration with a brisk diuresis at times when they are either unresponsive or poorly responsive to injections of a mercurial diuretic. This is the only situation in which we

have found that Diamox might be effective where mercurial diuretics, parenterally administered, were not. Generally, cardiac patients with refractory fluid retention who will not respond to mercurial injections will not respond to Diamox.[4,10,11]

CONCLUSIONS

1. In 21 ambulatory cardiac patients who had required mercurial injections, Diamox administered as one 250 mg. tablet of Diamox every other day proved equally satisfactory in maintaining optimal body weight.

2. In this dosage no side effects or significant alterations in plasma electrolyte concentrations were observed.

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Clinical Reports

DOUBLE ATRIAL STIMULATION WITH RECIPROCAL RHYTHM

KONSTANTINE S. ZAKOPOULOS, M.D.

ATHENS, GREECE

RECIPROCAL rhythm is a rare disturbance of the cardiac mechanism, the first case of which was published by White[1,2] some forty years ago. In 1943, Decherd and Ruskin[3] reviewed 22 cases in the literature and added another 3 of their own. Later, Bix[4] raised the number of cases reported to 30, adding another 4 of his own. Since that time 3 other cases have come to our knowledge, those of Pick and Langendorf,[5] Christensen and Andersen,[6] and our first case.[7]

In the majority of these cases the basic rhythm was a nodal rhythm, but, as Bix has stressed, some of them[4,8,9,10] occurred in a sinus rhythm. This was found also in our first case.

Double atrial stimulation showing two inverted P waves within one couplet was reported by Decherd and Ruskin[3] in their Case 3. The first P was the result of rapid retrograde conduction to the atria, the second one, having a long R-P interval, giving rise to a reciprocal ventricular beat. This was a unique case in the literature.

The case presented below is another example of this rare phenomenon.

CASE REPORT

P. J., a 40-year-old man, complained of palpitation and of periodical sensation of flutter in the precordium. These symptoms appeared for the first time 15 years before. Slight at first, they had become serious and frequent at the time of examination.

The physical examination was negative for all the systems except the circulatory. The heart was within normal limits on percussion and the apex beat was in the fourth intercostal space at the mid-clavicular line. Blood pressure was 120/80 mm. Hg. The pulse rate was irregular because of bigeminas, trigeminas and short runs of beats, usually six to eight. On auscultation there were no murmurs. Fluoroscopic and x-ray examinations were negative.

Since the patient was followed for a period of four months, we were able to take many ECG's at rest, before and after some trials and drugs. Unfortunately, the patient's collaboration was poor, because he refused to enter the hospital or take injections. He also did not accept quinidine because of side effects experienced in the past.

Electrocardiographic Records.—In Fig. 1 from top to bottom are shown two strips at rest, two after exercise, two after eye-globe pressure, and one Lead V_1 at rest. In the strips *A*, *B*, *C*'

From the Laboratory of Pathological Physiology, the National University of Athens, Greece.
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and *D*, bigeminas, trigeminas, and one tetragemina are seen, introduced by a sinus beat. The ectopic beats are characterized by a negative atriogram which usually follows and sometimes coincides with the preceding T wave.

In some instances, as in the first and last bigeminas of *B* and the two first trigeminas of *C*, the first ectopic beat presents an "additional negative wave" after QRS and before the T wave. On the other hand, the QRS of the first ectopic beat shows frequently an aberration which is due to defective conduction of the right bundle branch, associated with secondary T-wave changes. This is clearly shown in the last strip, *G*.

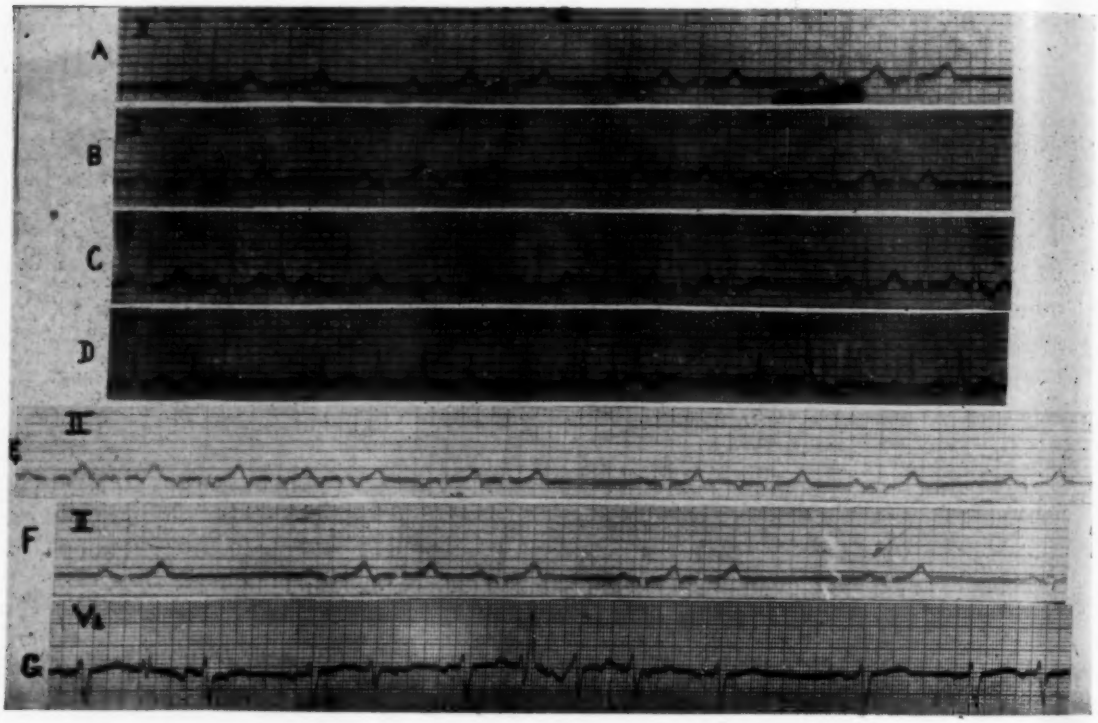

Fig. 1.—*A* and *B*, at rest; *C* and *D*, after exercise; *E* and *F*, after eye-globe pressure; *G*, Lead V_1 at rest. (See text for explanation.)

E and *F* are fragments of a continuous record and were taken a short time after reflex vagal stimulation via eye-globe pressure. At the beginning of *E* a short paroxysm of tachycardia is seen, consisting of ectopic beats and presenting negative atriograms with the constant presence of "additional negative waves" between QRS and T. After the vagal stimulation the expected bradycardia occurred with probable movement of the pacemaker within the sinus, as one can suspect from the altered shape of the sinus P waves. However, some of the bigeminas persist.

The upper five strips (*A*, *B*, *C*, *D*, and *E*) of Fig. 2 and Fig. 3 represent strips of continuous records taken in Lead II and III, respectively. Bi- and trigeminas are rarely seen and the predominant feature is that of the short paroxysms of tachycardia, characterized by the negative atriograms and the frequent presence of additional negative waves.

Strip *F* of Fig. 2 has been taken after digitalis and *G* after belladonna. In *F*, bi- and trigeminas interrupt the normal function of the sinus. In *G* the arrhythmias have disappeared, and only rare ectopic beats—two of them are seen in the strip—interrupt the restored sinus rhythm.

The last two strips, *H* and *I*, represent a continuous record taken after belladonna was stopped. The arrhythmia reappeared in the type of the short paroxysms with multiple additional negative waves. During the time of taking this record the arrhythmia stopped abruptly and the normal

rhythm was restored in a long ECG (not presented here) which was taken that day, as well as in the ECG taken during the two following days.

DISCUSSION

The characteristic elements of the arrhythmia in this case are two: that of ectopic beats in the type of bigeminas, trigeminas, and short paroxysms of tachycardia, and that of additional negative waves.

In the bi- and trigeminas the ectopic beat seems at first glance like an atrioventricular extrasystole arising in the upper nodal area of Zahn (P-R = 0.10—0.12 sec.). However, in some instances P–R of the ectopic beats is greater than 0.12 sec., reaching the values of 0.14, 0.16, 0.18 sec. (Fig. 3, $R_{3,10,19,32}$). There is no doubt that the additional negative wave is atrial in origin because of its chronological and morphological appearances and proves an additional retrograde stimulation of the atria. Whenever it falls between QRS and T, it gives a characteristic picture to the ECG, with two inverted P waves between two ventriculograms. In other instances in which it appears after the preceding QRST represents a typical example of reciprocal rhythm with a "negative P wave sandwiched between two QRS"[2] (Fig. 3, negative P between $R_{4-5,\ 5-6,\ 8-9,\ 14-15}$).

Based on these instances one can certainly exclude the existence of a parasystolic focus with low atrial localization and partial 2:1 A-V block. This is also true because of the time appearance of the negative P waves, which is inscribed in Fig. 3 throughout the whole record.

Paroxysmal atrial flutter with 2:1 A-V block is to be excluded by the lack of the characteristic picture of flutter, the existence of the isoelectric line,[12] the characteristics of typical reciprocal rhythm, and the result of reflex vagal stimulation (Fig. 1), which did not unmask hidden flutter.[13]

Consequently, guided by the cases of reciprocal beats we proceeded to give the following interpretation, complete and unique, to the arrhythmia of this case (see Fig. 3). From the sinus the stimulus moves downward to the A-V node, giving rise to the first QRST. The stimulus, finding a pathway above the region of the A-V node, returns to the atria (retrograde), which have already recovered and produces the first negative P wave. It then proceeds to move again downward (antegrade), giving rise to the second QRST. This short circular movement produces the bigeminas and trigeminas.

In some bigeminas as well as in the cases of short paroxysms of tachycardia the phenomenon of double atrial stimulation is present, as can be seen from the two negative P waves. This is extremely rare, since there are only two such cases reported, those of Danielopolu and Proca,[14] and Decherd and Ruskin.[3]

After Mines'[15] classical experiments on the frog and rayfish, and after White's[1,2] and Drury's[16] publications on reciprocal rhythm, Scherf and Schookhoff[17] succeeded in reproducing reciprocal beats on the dog as "return extrasystoles" (Umkehr extrasystolen). Scherf[18] expressed the concept of functional longitudinal dissociation of the nodal tissue because "according to the law of absolute refractoriness it is impossible for the stimulus to pass through the same bundle twice in a so rapid succession." Later, Schmitt and Erlanger's work[19] confirmed the idea and led to its adoption. However, Decherd and Ruskin,

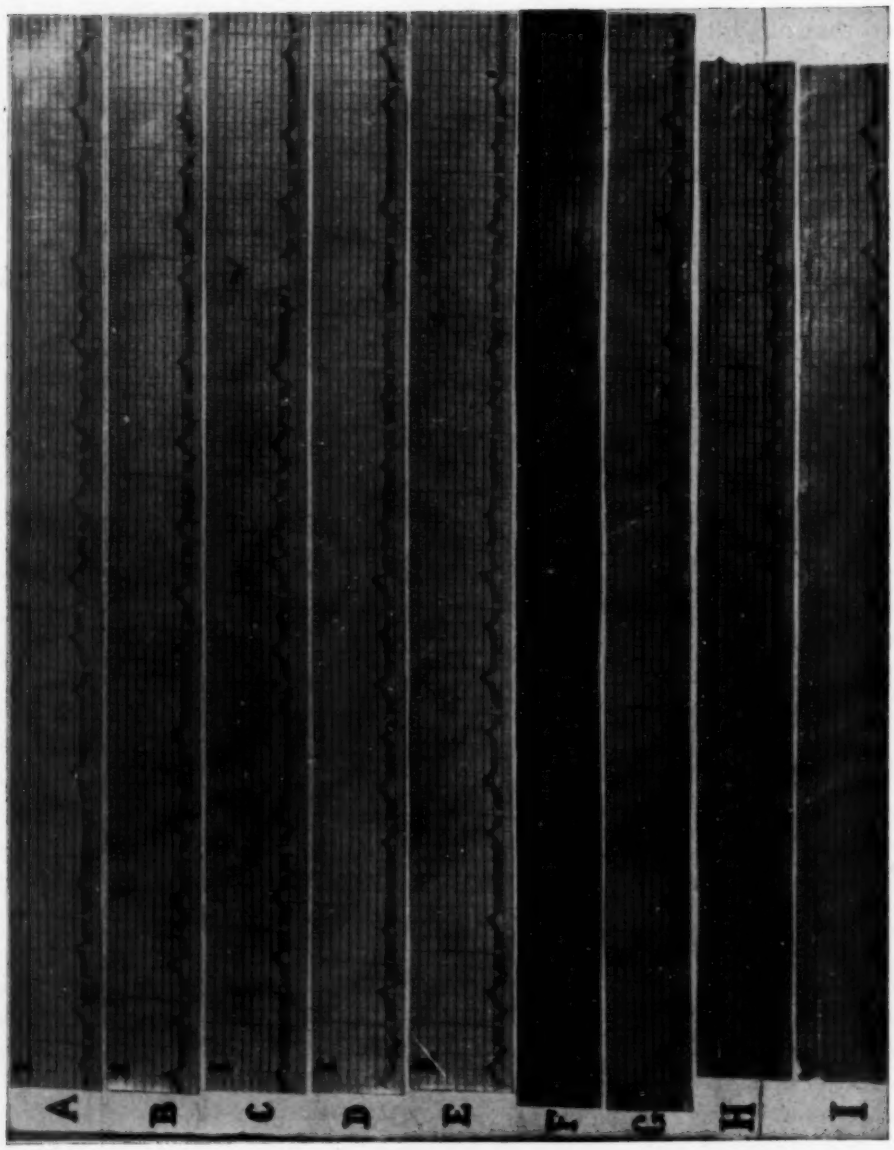

Fig. 2.—*A* to *E*, Continuous record taken the same day as that of Fig. 3; *F*, after digitalis; *G*, after belladonna; *H* and *I*, continuous record taken after belladonna was stopped. Reappearance of the arrhythmia and sudden restoration of the normal rhythm (*x*).

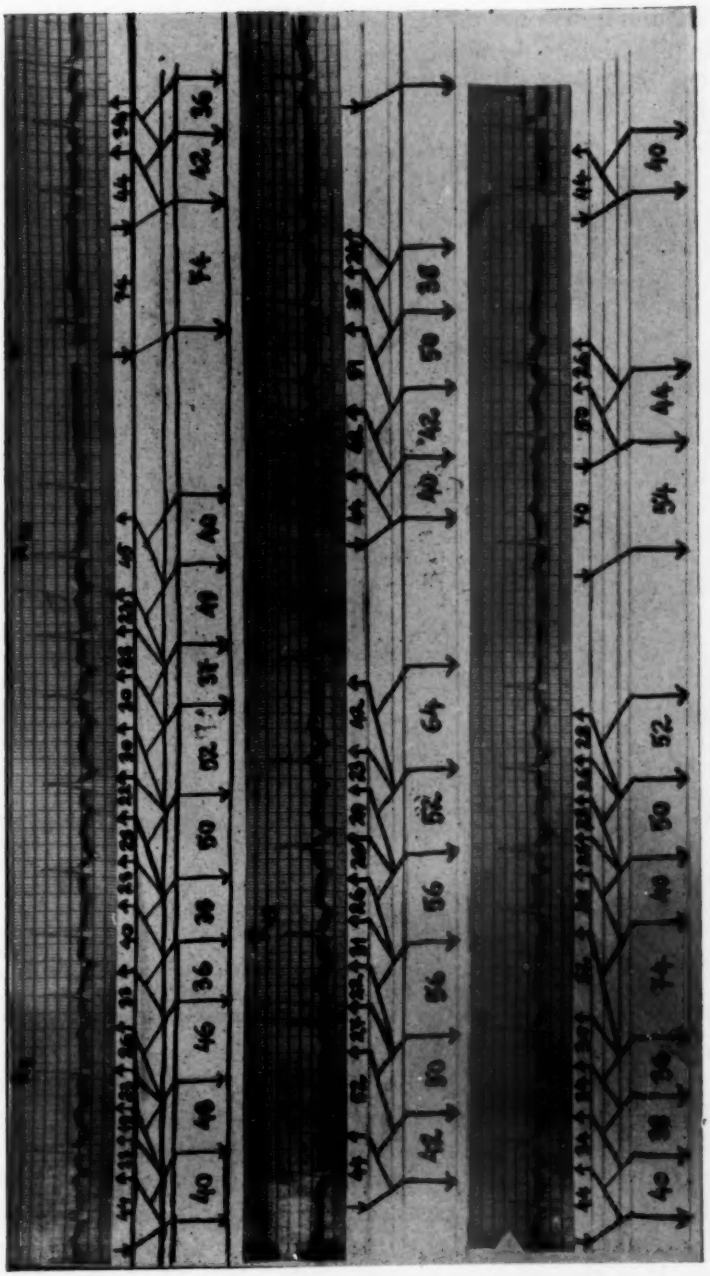

Fig. 3.—Continuous record (Lead III). Discussed in text.

finding the above conception insufficient, expressed another hypothesis for the explanation of their case, which presented double atrial stimulation in the same couplet. According to these authors, "above the A-V node and near the junction of the nodal tissue with that of the atrium, or more likely, at the junction of the atrial and ventricular portions of the A-V node, there is an area of refractory tissue of varying size and shape and/or in varying stages of recovery, and through which conduction will take place in varying directions and at varying rates" (Fig. 4).

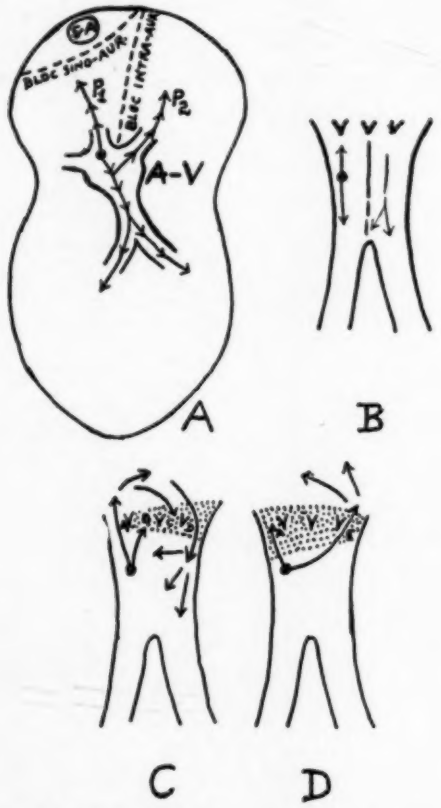

Fig. 4.—Schematic illustration of the hypothesis proposed by Danielopolu and Proca of functional intra-atrial block (*A*), the concept expressed by Scherf of functional longitudinal dissociation (*B*), and the hypothesis of Decherd and Ruskin of varying size and shape, area of refractoriness (*C* and *D*).

We have found this last hypothesis compatible with the case presented. Accordingly, we believe that after the discharge of the A-V node the stimulus finds two pathways of varying refractoriness leading to the atria and moves through the one rapidly, through the other with slowed conduction. As a result, a double successive activation of the atria ensues. After the first one, the stimulus, moving again downward via one of the free pathways, finds the A-V node and/or the tissues below it in the refractory state, and so it is blocked and remains unanswered. However, after the second activation, the node or the bundle of His has recovered completely and the forward conduction is rapid with a short P-R interval, within the limits of 0.12 sec. In some cases the stimulus, moving upward and unable to use the first pathway because of refractoriness greater in

intensity of extent, uses the second one. A long R-P interval is then inscribed and a "negative P wave sandwiched between two QRS complexes"[2] appears.

The same can happen, of course, in the case of use of the first pathway, provided this is in a relative refractory period. In this case R-P will also be long. The differentiation of the above two circumstances will be determined only upon the forward conduction. If this (P-R) is short it will support the view of use of the second pathway with the longer R-P. If on the other hand, it is long, the pathway used for the forward conduction is most probably the first one. In this last condition the case cannot be excluded in which the second pathway with long R-P has been used, provided that the forward conduction has traveled through a relatively refractory tissue, resulting in a long P-R interval. This last possibility, without being excluded, must be rare, as it is proved in the curve shown in Fig. 5.

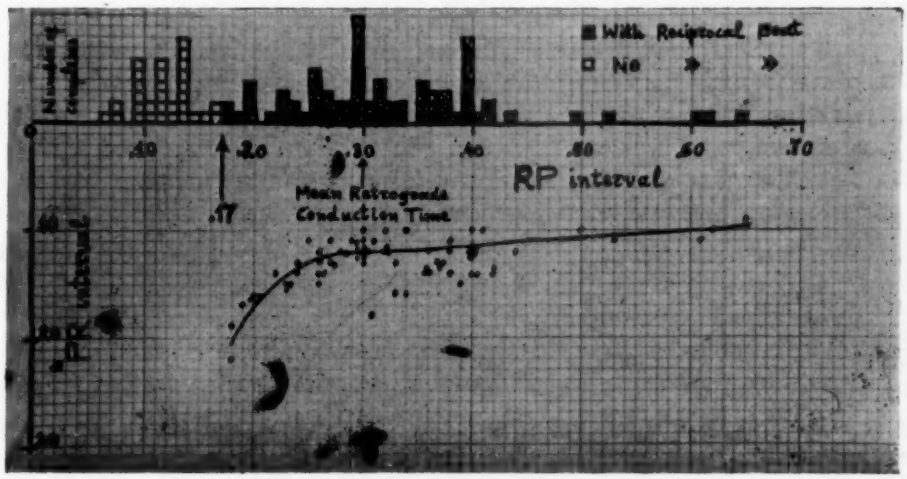

Fig. 5.—Diagrammatic representation of the complexes of ectopic origin found in Fig. 2,*A* and *B*. R-P intervals are plotted against P-R according to the method used by Decherd and Ruskin. The times concerning R-P and P-R intervals of the complexes followed by reciprocal beats give a smooth curve. (See text for further details.)

"The simplest and most convincing evidence of a re-entry mechanism in the human heart is the phenomenon of reciprocal beating in cases of auriculoventricular nodal rhythm with delayed retrograde conduction."[5] For some authorities the first requisite for the existence of a reciprocal rhythm is the location of the cardiac pacemaker in the A-V node. However, after the communication of cases of reciprocal rhythm in a basic sinus rhythm, it seems possible (Bix[4]) that many cases remaining undiagnosed are taken as A-V or atrial extrasystoles. A proof of this fact is the case here presented, in which the basic rhythm is a sinus rhythm.

Double atrial stimulation in our case is observed rarely after isolated ectopic beats and most frequently during the short paroxysms of tachycardia.

In Fig. 5 all the complexes of ectopic origin found in Fig. 2 (*A*, *B*, *C*, *D*, and *E*) and Fig. 3, followed or not by reciprocal beat, are plotted against the P-R

and R-P intervals, in the manner used by Decherd and Ruskin. The smooth curve drawn through the points closely resembles that of Decherd and Ruskin,[3] Lewis and Master,[20] and Drury and Regnier.[21]

In this figure the absolute refractory period is clearly discerned at 0.17 sec. Whenever retrograde conduction is short, the reciprocal beat does not occur; whenever it is long, the reciprocal beat appears and obeys the rule of interrelationship of the R-P and P-R intervals. The absolute refractory period of the junctional tissue to forward conduction was found to be 0.26 sec. by Decherd and Ruskin in their case. This time represents the upper limit noted in several cases, the lower being estimated at 0.11 sec.[3] The period of relative refractoriness extends in our case up to 0.42 sec. and the mean retrograde conduction time to 0.30 sec. Similar values have also been observed by Decherd and Ruskin, i.e., 0.44 sec. and 0.30 sec., respectively.

The patient, ambulatory and poorly cooperating, permitted only a few experiments to be performed. Exertion has many times given the same results, i.e., increasing activity of the sinus and some shortening of the retrograde conduction.

Vagal stimulation was tested by using eyeball pressure during a short paroxysm of tachycardia (Fig. 1, *E* and *F*). The tachycardia was stopped, a slow sinus rhythm was restored, the double atrial stimulation and the reciprocal beats disappeared, and the retrograde conduction, at the beginning at least, was greatly slowed (Fig. 1, *E*). These results generally agree with those of other authors,[3,14] but, lacking confirmation by repetition and usage of cholinergic drugs, their value necessarily is diminished.

Digitalis is known to lengthen retrograde conduction,[22] causing reciprocal beats or increasing their frequency. Decherd and Ruskin with beginning digitalization found backward conduction on the average more rapid. Increasing dosage caused marked delay in retrograde conduction, though this too fell sharply when the drug was stopped. Our patient, an outpatient, was not followed closely while taking digitalis. However, his ECG after 1 mg. Digitaline Nativelle (10 drops daily for 6 days) showed no alteration (Fig. 2,*F*) as to the retrograde conduction and the bi- and trigeminas. It is possible that digitalis was given in inadequate quantity or too slowly, so that it was unable to exert any influence upon the arrhythmia.

The patient forbade injections and it was impossible to test atropine. Therefore we give him belladonna tincture 60 drops daily for five days. The ECG taken on the sixth day was normal and showed a small increase in rate and rare ectopic beats (Fig. 2,*G*). This result confirms the observation of several authors in clinical cases of reciprocal rhythm, where atropine shortened consistently the retrograde conduction with the consequent disappearance of the reciprocal beats. The patient of Decherd and Ruskin, when atropine was given after Prostigmin, showed actual acceleration of conduction and shortening of the refractoriness and the recovery.

A fact of difficult explanation is the reappearance of the arrhythmia twenty days after the belladonna was discontinued and its abrupt disappearance two days later under the electric control, with a complete restoration of the normal

sinus rhythm (Fig. 2,*H* and *I*). However, we suggest that this is in favor with the fundamental role of the functional cause which precipitated the complex mechanism underlying this curious arrhythmia.

CONCLUSION

The conclusion seems justifiable that, in an otherwise normal person, from time to time, without any apparent cause and after some functional disturbance in the A-V junctional tissue, the curious phenomenon was born, i.e., the impulse upon reaching the A-V node was propagated through the normal pathway and abnormal ones as well, which resulted in bigeminas and trigeminas and at times in double atrial stimulation with reciprocal rhythm, and short paroxysms of tachycardia.

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CONGENITAL HEART DISEASE AND ACUTE MYOCARDIAL INFARCTION

II. Course and Necropsy

HARRY VESELL, M.D.

NEW YORK, N. Y.

IN THE first published case of congenital ventricular septal defect and acute myocardial infarction the diagnosis was made on clinical data only.[1] Recently the patient died at the age of 37 years, and a post-mortem examination was made. The purpose of the present communication is to give a progress report since the original publication and to describe the necrospy findings.

After convalescence from the acute myocardial infarction of February, 1953, the patient gradually resumed his regular work as an insurance broker. Eight months later he returned to the hospital for surgical treatment because of the attacks of appendicitis. The appendix was found thickened, edematous, with evidence of recent inflammation; the pathological report was subacute periappendicitis.

One year after the acute coronary episode examination revealed few additional cardiac changes. Some increase in size of the heart, probably of the left ventricle, was evident on fluoroscopy and on the electrocardiogram. Few serial changes in the signal abnormalities were noted from those in the stabilized early postcoronary tracings. He continued at his regular work without medical complaints until Dec. 20, 1955. On that day, a very cold one, while driving his automobile, he felt some pains in the lower substernal regions, with chills, fever, and sweating. These lasted about 3 to 4 hours. About 5 days later he had some unusual shortness of breath upon exertion, and an awareness of his heart beating. Because of persistence of these complaints and the presence of a sensation of heaviness in the lower substernal region, he was admitted to the hospital on Jan. 4, 1956. Here, examination revealed the cardiac findings as previously described,[1] with a sinus tachycardia, further increase in size of the heart, and evidence of left ventricular failure but not of a fresh myocardial infarction. Of special note among the laboratory data was the blood cholesterol of 350 mg. per cent with esters of 230 mg. per cent. After several days of treatment for cardiac failure, the symptoms and signs of the failure disappeared.

He was discharged from the hospital on January 17, 23 days after the onset of the chest distress and continued treatment at home. In the next 4 days on incomplete bed and chair rest he appeared to be doing well and there were no complaints. On Jan. 21, 1956, while he was seated at home doing some bookkeeping, his wife went out to do her shopping. When she returned about 1 hour later, he was found on the floor dead. The body was removed to the Beth Israel Hospital where an autopsy was performed.

The pertinent findings on necropsy were as follows: The body was that of a well-developed and well-nourished white young man, measuring 66 inches and weighing approximately 160 pounds. The chest contour was not unusual. Both lungs were well expanded. The right and left lungs weighed 750 and 450 grams, respectively. Both pleural cavities were free of effusions and adhesions. The trachea and bronchi had markedly injected mucosa and contained red-brown mucous material.

From the Department of Medicine and Cardiographic Laboratory, Beth Israel Hospital, New York City.

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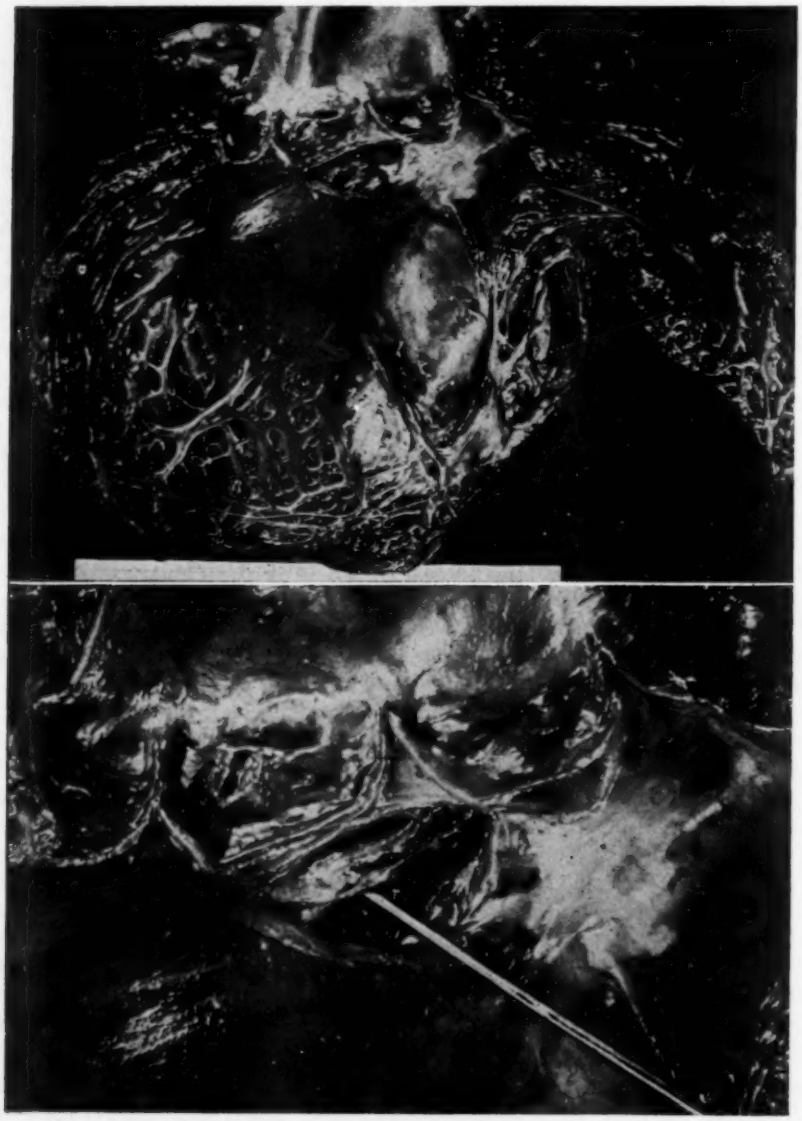
Heart.—The heart weighed 620 grams. The pericardial sac contained about 50 c.c. of clear amber fluid. The pericardial surface was smooth and glistening. The venae cavae entered the right atrium in their usual manner. The right atrium was markedly dilated. The endocardium was smooth and opaque. The foramen ovale was closed. The right auricular appendage was free of thrombi. The coronary sinus was patent. There was a Chiari's network at its entrance. The tricuspid valve ring measured 13.2 cm. in circumference and appeared incompetent. The posterior and posterior half of the septal leaflet were thin, smooth, and translucent. The region of the commissure between the septal leaflet and the anterior leaflet was thickened for a distance of 2.0 cm. Here the septum membranaceum and the leaflets were one and had three perforations ranging from 0.2 to 0.6 cm. in diameter (Fig. 1). The chordae tendineae here were shortened, thickened, and fused. The right ventricular aspect of this perforated band was roughened, trabeculated, and convex. The adjacent portion of the anterior leaflet was also thickened and roughened. Its chordae tendineae were thickened. The right ventricle was markedly dilated (Fig. 2). The endocardium was smooth and glistening except for a few gray, opaque areas measuring up to 1.0 cm. in diameter near the undefended space. The red-brown right ventricular myocardium measured up to 0.4 cm. in thickness. The pulmonary valve ring measured 9.0 cm. in circumference. The pulmonary valve cusps were thin, smooth, and translucent. The corpora arantii were not prominent. The pulmonary artery contained several atheromatous foci but were free of thrombi and emboli. The pulmonary veins entered the left atrium in their usual manner. The left atrium was slightly dilated; its endocardium was smooth and opaque. The left auricular appendage was free of thrombi. The mitral valve ring measured 11.2 cm. in circumference. The valve leaflets contained interdigitating nodularities. The chordae tendineae were thin and delicate. The anterior papillary muscle was robust. The posterior papillary muscle was thin, atrophic, and contained numerous gray streaks. The left ventricle was aneurysmally dilated and its endocardium was markedly opaque. The myocardium here contained numerous gray streaks and measured up to 0.5 cm. in thickness. The ventricular septum measured up to 2.0 cm. in thickness. At the site of the undefended space there was a 2.0 cm. area which bulged about 0.5 cm. into the right ventricle. It contained the three perforations described above. Its surface was roughened, gray, and trabeculated. The aortic valve ring was normal in location and measured 7.0 cm. in circumference. The valve cusps were thin, smooth, and translucent. The corpora arantii were not prominent. The commissure between right and left cusps was fused. The sinuses of Valsalva contained a few atheromatous foci. The coronary ostia were widely patent. The right circumflex artery contained several atheromatous foci 3 cm. from the origin where the lumen was duplicated, narrowed for a distance of 1.5 cm., and recanalized. The right circumflex was traced beyond the posterior interventricular sulcus. The left coronary contained a few atheromatous foci but was patent as far as it could be traced. It had an eccentric lumen in places. The left circumflex contained a few atheromatous foci but was patent throughout. It was very short, of small caliber, and had a flexible wall. It could not be traced to the posterior interventricular sulcus. The right circumflex was of much larger caliber than the left circumflex and supplied the major portion of the posterior surface of the heart. The aorta contained several atheromatous and a few calcified foci; they were most marked in the abdominal aorta. It was free of thrombi and emboli. The venae cavae were not dilated and were free of thrombi and emboli. There was no fluid in the peritoneal cavity. The liver weighed 1,990 grams. The brain weighed 1,800 grams and appeared normal on gross examination.

Microscopic.—The posterior mitral valve leaflet was diffusely thickened. The anterior leaflet of the mitral valve contained many atheromatous areas. The septal leaflet of the tricuspid valve and the septum membranaceum contained atheromatous foci. The anterior leaflet of the tricuspid valve was markedly thickened by atheromatous deposits. The left aortic valve cusp contained many atheromatous areas. The subendocardial tissue of the left ventricle was thickened. The myocardium of the left ventricle contained areas of interstitial and perivascular fibrosis. The left posterior papillary muscle was replaced by fibrous tissue. The myocardium of the interventricular septum contained numerous areas of interstitial and perivascular fibrosis. The right circumflex coronary artery, 4 cm. from its origin, showed the intima thickened and containing calcific foci. The right circumflex 10.5 cm. from its origin showed the intima slightly thickened and the lumen contained post-mortem clot. In the left anterior descending artery, 0.5 cm. from its origin,

the intima was thickened by atheromatous foci and the lumen was eccentric. The intima of the left circumflex, at 0.5 cm., was thickened and contained calcific areas. The lumen was widely patent.

Liver.—There was increased fibrosis with lymphocytic aggregates and hemosiderin pigment beneath Glisson's capsules and about its central veins. The central veins were markedly congested.

A.



B.

Fig. 1.—*A*, Left ventricle showing marked dilatation and hypertrophy; aortic valve is seen: underneath it the membranous septum with defect. For further description see text. *B*, Higher magnification of aortic valve area and membranous septum; probe is in the defect.

Spleen.—The capsule was smooth. The pulp was markedly congested. A moderate number of eosinophilic leukocytes were seen throughout.

Kidney.—The kidney was markedly congested.

Adrenal.—The internal layer of the cortex was markedly congested.

Lung.—There was marked congestion of pulmonary arteries. There were numerous foci of pulmonary edema with a collection of heart-failure cells. The bronchi contained many leukocytes and lymphatic cells. The musculature of the pulmonary arterioles was not hypertrophied.

Thyroid.—There was a colloid adenoma in the thyroid.

The pathological findings in the heart can be divided into two parts: (1) the malformations of the membranous interventricular septum and the tricuspid valve, and (2) the pathologic changes in the coronary arteries and myocardium.

The pars membranaceum varied somewhat from the usual appearance in cases of ventricular septal defect (V.S.D.). There was some bulging toward the right ventricle and the holes were 3 in number. The diagnosis of a congenital V.S.D. rather than aneurysm with perforations was made for the following rea-

Fig. 2.—Right ventricle with marked dilatation and hypertrophy. Tricuspid septal leaflet with hole in it, through which probe emerged. For further description see text.

sons. The history indicated that the loud Roger murmur was present from early infancy, with this murmur being heard on each occasion of the many examinations made by the author over the past 25 years. There was no history of an illness such as subacute bacterial endocarditis, nor were the pathological findings indicative of this condition. Therefore, it was not considered to be the cause of the bulging of the membranous septum or of the perforations. Furthermore, aneurysm of the membranous septum as described by Mall[2] and others[3,4] connotes a comprehensive series of local embryonal developmental failures of the heart. These include failure of shift of the inferior ventricular septum to the right; failure of shift of the initial ascending aorta to the left; a resultant bulge of the pars membranaceum well (1 to 2 cm. or more) into the right side, often into the right atrium; and, at times, formation of a large multilocular sac.[3] The anomalous

position of the aorta causes the membranous septum to take a horizontal rather than the normal vertical position. In our case there appeared to be no abnormality in position of the inferior interventricular septum nor of the beginning of the ascending aorta, nor was the membranous septum in the horizontal position. It bulged about 0.5 cm. toward the right ventricle.

The deformation of the medial cusp of the tricuspid valve is explainable as a congenital malformation rather than an acquired disease or inflammation. The right tubercle of the A-V canal cushion which contributes to the membranous position of the ventricular septum also contributes to the formation of the tricuspid valve leaflets,[5,6] and so the septal leaflet may be deformed with developmental defects of the ventricular septum. Maude Abbott,[7] Marquis,[8] and Edwards[9] noted that some deformity of the tricuspid leaflet commonly exists in the vicinity of a V.S.D. A case of defect in the septal cusp of the tricuspid valve with a defect in the membranous septum was described in considerable detail by Gutzeit.[6] It was the only such case he was able to find in the entire literature (up to 1922). In his case, as in ours, the tricuspid valve was thickened, perforated, and up against the defect in the membranous septum which bulged into the right ventricle. His illustrations, *Abb. 1* showing the septal defect (single) as seen from the left ventricle, and *Abb. 2* showing the defect through the medial tricuspid leaflet as seen from the right ventricle, are similar to our Figs. 1, *A* and 2. He felt that its circumscript character, its flatness, without histological evidence of inflammation, as well as the presence of the V.S.D., all supported the congenital origin of the deformity of the tricuspid leaflet. Gutzeit,[6] discussing with Geipel the theories of development failure to account for changes in the tricuspid valve, was of the opinion that the "arrest malformation" of the medial cusp of the tricuspid was a "Bestehenbleiben des primar endothelrohres" and due to a lack of differentiation involving the right tubercles of the coalescing endocardial cushions, with tricuspid insufficiency playing an important role. He considered the tricuspid valve changes and the ventricular septal defect as separate malformations, both congenital, associated with arrest in embryonal development of this region of the heart. Later, reports of other cases with malformation of the medial cusp of the tricuspid valve in association with V.S.D. and without inflammatory changes, gave additional support to the hypothesis of a congenital malformation as the explanation of the tricuspid as well as of the septal abnormalities. Weinstein[10] described a case of congenital malformation of the medial leaflet of the tricuspid valve which was "brought up somewhat tightly against the defect in the membranous septum." He, too, thought that embryonal development of the tricuspid leaflet was associated closely with that of the membranous ventricular septum, and was responsible for the pathology there. Tricuspid valve deformities accompanying V.S.D. were also described by Hemsath and associates,[11] Perry and associates,[12] and Lillehei and associates.[13] However, in a review of pertinent literature, I was unable to find a case identical to ours in the small septal bulge, the three perforations or defects in the membranous septum, and the changes in the tricuspid valve.

The effect of V.S.D. on the coronary vessels is of interest. As previously

stated, little data on this subject could be found in the literature.[1] Recently, a survey on the coronary vessels at autopsy in 60 cases of congenital heart disease of many varieties, including V.S.D., was reported.[14] The age of the patients ranged from 3 months to 27 years. Macroscopically, no changes were observed in the coronary arteries, though the authors believed that the orifices and main branches were relatively narrow in proportion to the size of the hypertrophied ventricles and the heart weight. On angiography, the first and second grade branches appeared relatively wide. Microscopically at 30- to 60-fold magnification, the coronary arteries and veins appeared considerably dilated. They were not increased in number. In another recent report of a case of V.S.D. (with prolapse of an aortic valve cusp), the coronary arteries of a 57-year-old man at autopsy were described as normal in origin and distribution.[15]

In our case, the origin and orifices of the coronary arteries were normal. The left circumflex was smaller and the right circumflex was larger than usual. Dilatation and hypertrophy of the vessels were not seen. There were some scattered, but not severe, atheromatous foci in the coronary arteries and a few in the main left and in the short left circumflex branch but the lumen was patent as far as could be traced in the gross specimen. The right circumflex was larger than the left circumflex and contained several large atheromatous foci, 3 cm. from the origin where the lumen was duplicated and narrowed for a distance of 1.5 cm. Here was a recanalization of an old occlusion which was believed to account for the area of infarction with aneurysmal dilation of the posterior and posterior septal wall of the left ventricle. On the anterior wall of the right ventricle in the vicinity where the right coronary had been occluded there was an area of dull greyish fibrous tissue (Fig. 2). This "jet" lesion was in direct line with the hole low in the tricuspid medial cusp and the defect in the membranous septum. Through these defects a stream of blood flowed under left ventricular pressure, at least during ventricular systole. In the absence of such severe atherosclerosis elsewhere in the coronary arteries, a connection was suggested between the stream of blood shunted through the defects, the "jet" lesion in the opposite right ventricular wall, and the enhancement of the atherosclerotic changes in the overlying right circumflex coronary artery. In the case of a 3-year-old child with V.S.D. reported by Kroop and Grishman,[16] the blood stream through the defect "hollowed out" a portion of the anterior wall of the right ventricle.

Recently, it was observed by Wood and associates[17] that V.S.D. is neither so common nor so innocent as is generaly believed. In reviewing all cases of congenital heart disease at the National Heart Hospital and at Brompton Hospital since 1948, they were impressed with the infrequency of the classical *maladie de Roger* type encountered. Of their 750 cases of congenital heart disease only 8 per cent had isolated V.S.D., thus placing it fifth in order of frequency. In the majority of cases sent to them with this label the diagnosis proved wrong. Of 60 cases, 40 with catheter studies and a doubtful one excluded, only 3 were between 30 and 40 years of age and 2 were over 40 years. Similar rarity of individuals over 30 years of age with this condition was also noted in other recent studies; in a series of 32 cases of isolated V.S.D. reported by Marsico and associates,[18] only 4 patients were over 20 years of age, the oldest being 29; in the

series of Blount and associates,[19] of 23 cases with the diagnosis confirmed by catheterization only 2 patients were over 30 years of age, the oldest being 36 years; of DuShane's[20] patients the oldest was 29 years. In the series of Downing and Goldberg,[21] 8 of the 100 patients were over 30 years old, 5 were between 30 and 40 years old, 3 were 40 years or more. Thus in the 6 series of cases of V.S.D. mentioned above* less than 10 per cent of the 333 patients were over 30 years of age. Although there may have been a factor of selection (not age) in some of the series, the over-all paucity of adults over 30 years of age with V.S.D. indicates nevertheless that patients with this defect do not live long into adult life because of this lesion and its complications. This signifies a seriousness not generally recognized previously. The more serious nature of the condition was noted in some recent reports.[22,23,24]

In the case reported, the V.S.D. appeared to contribute toward early atherosclerotic coronary occlusion; and after the myocardial infarction, to contribute to the production of aneurysmal dilatation of the left ventricle with progressive cardiac enlargement, failure, and death.

SUMMARY AND CONCLUSION

The subsequent course and necropsy findings have been described here in the first published case of congenital V.S.D. with acute myocardial infarction. Defects were found in the membranous septum and in the septal cusp of the tricuspid valve. There was some bulging of the pars membranaceum. The changes were considered related embryonal malformations due in part to arrest in development from the A-V endocardial cushions. Differential diagnosis from aneurysm of the ventricular septum with perforations was discussed. This condition could not be excluded. A relationship was suggested between the V.S.D., the coronary occlusion, and the aneurysmal dilatation of the left ventricle. The infrequency of uncomplicated V.S.D. was mentioned. The paucity of patients over 30 years of age and other observations noted indicated a more serious outlook not generally recognized and suggested some modification of criteria toward more liberal selection of cases for surgical treatment.

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*Includes Seltzer's series.[1]

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PAROXYSMAL ATRIAL TACHYCARDIA WITH A-V BLOCK: REPORT OF A CASE WITH UNUSUAL ORTHOSTATIC EFFECTS

JAMES E. KREISLE, M.D., AND MATTHEW F. KREISLE, SR., M.D.

AUSTIN, TEX.

PAROXYSMAL atrial tachycardia with A-V block has recently received emphasis as a manifestation of digitalis intoxication.[1,2] We have encountered an instance of this arrhythmia, unrelated to the use of digitalis, in which progressive alteration in the degree of A-V block occurred in response to change of posture. As we have discovered only four previously reported instances of this phenomenon, it is felt worth while to present our observations in this case.

CASE REPORT

A. B. M., a 78-year-old widow, consulted us in June, 1954, and October, 1955, because of occasional brief episodes of weakness associated with vague anterior thoracic distress; at times a "skipping" of the pulse had been noted. Physical and routine laboratory examinations were not remarkable except for a faint apical systolic murmur, a few dry, crepitant râles scattered throughout the chest, and an intermittently irregular pulse with a rate of 60 to 68 per minute. The blood pressure readings were 134/64 and 144/70 mm. Hg. An electrocardiogram recorded in October, 1955, was interpreted as showing multiple atrial extrasystoles. No medication was prescribed.

Aside from occasional mild recurrence of the above symptoms, the patient did well until about 6:00 P.M. on March 30, 1956, when, after a period of stooping over and tearing heavy cloth, she developed vague anterior chest discomfort accompanied by mild faintness. She felt better on lying down and slept flat in bed throughout the night without incident. On arising, however, she again noticed the discomfort in her chest and was unable to stand and walk without nearly fainting.

Fig. 1 was recorded with the patient recumbent at 9:30 A.M. on March 31, 1956. It revealed an atrial tachycardia of 164 per minute with 3:2 and 4:3 A-V block; the Wenckebach phenomenon was present, and slight aberration of intraventricular conduction was indicated in the second or second and third complexes of each group of ventricular responses, especially in Leads II and III.

When the patient was then examined sitting upright, she appeared weak and languid; her radial pulse rate was found to be roughly 176 per minute and her blood pressure 86/66 mm. Hg. When she was allowed to recline again, her pulse rate quickly dropped to 82 per minute, remaining regular except for occasional periods of bigeminal or trigeminal rhythm. The blood pressure rose to 130/80 mm. Hg, and the patient ceased to feel faint. In Fig. 2, *a*, *b*, *c*, and *d* show, respectively, Leads I, II, III, and V_1, recorded with the patient recumbent; an atrial tachycardia of 164 per minute with 2:1 A-V block is clearly demonstrated except in Lead I, where the inconspicuousness of the P waves obscures the underlying mechanism. Fig. 2,*e* recorded immediately after assumption of the sitting position, shows the Wenckebach phenomenon with dropping of ventricular beats occurring prior to the eventual emergence of a 1:1 A-V ratio. In Fig. 2,*f*, recorded just after the patient was allowed to lie down again, reappearance of 2:1 A-V block with a ventricular rate of 82 per minute is shown.

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Fig. 3 shows sequential recordings of Lead V_1 in which are demonstrated the effects of postural change and of right carotid sinus pressure. Fig. 3,*a*, recorded with the patient recumbent, again shows atrial tachycardia of 164 per minute with 2:1 A-V block. Fig. 3,*b*, recorded just after a shift to the sitting posture, shows the first sign of decreasing A-V block, which occurred 13.6 seconds after the patient started up from the recumbent position and about 7 seconds after the sitting position had been attained; gradual transition from a 2:1 to a 1:1 A-V ratio is also shown in this strip. The tracings in Fig. 3,*c* and *d* were recorded as the patient continued sitting; considerable variation in the P-R interval (from 0.22 to 0.32 second) is present with but a single instance of dropped ventricular beat. Fig. 3,*e* shows an increase in the degree of A-V block during right carotid sinus pressure while the patient remained sitting. In Fig. 3,*f* the increased degree of A-V block (3:2 and 2:1) is shown to persist following release of carotid sinus pressure.

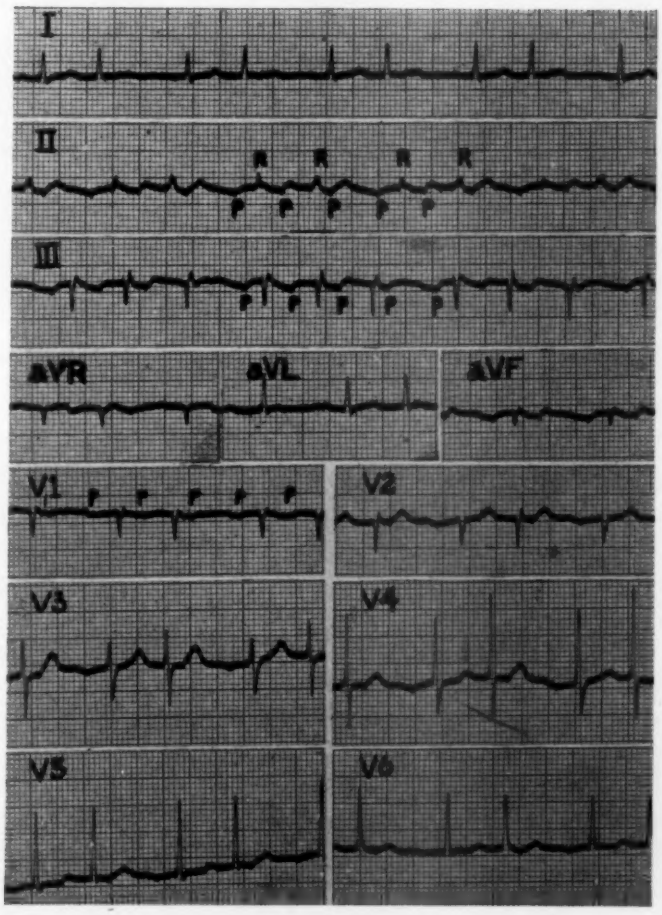

Fig. 1.—Paroxysmal atrial tachycardia, rate 164 per minute, with 3:2 and 4:3 A-V block, showing Wenckebach phenomenon and aberrant ventricular conduction. Patient recumbent.

The patient was given quinidine sulfate 0.2 Gm. orally every 4 hours. Fig. 4, recorded at 10:00 A.M. on April 1, 1956, following a total of 1.0 Gm. of quinidine sulfate, demonstrates restoration of sinus rhythm. The pulse record suggests that conversion occurred after 0.8 Gm. of the drug had been administered.

For a period of 4 weeks following discharge the patient was kept on a maintenance dose of 1.0 to 1.2 Gm. of quinidine sulfate daily. During this time she suffered two episodes of paroxysmal

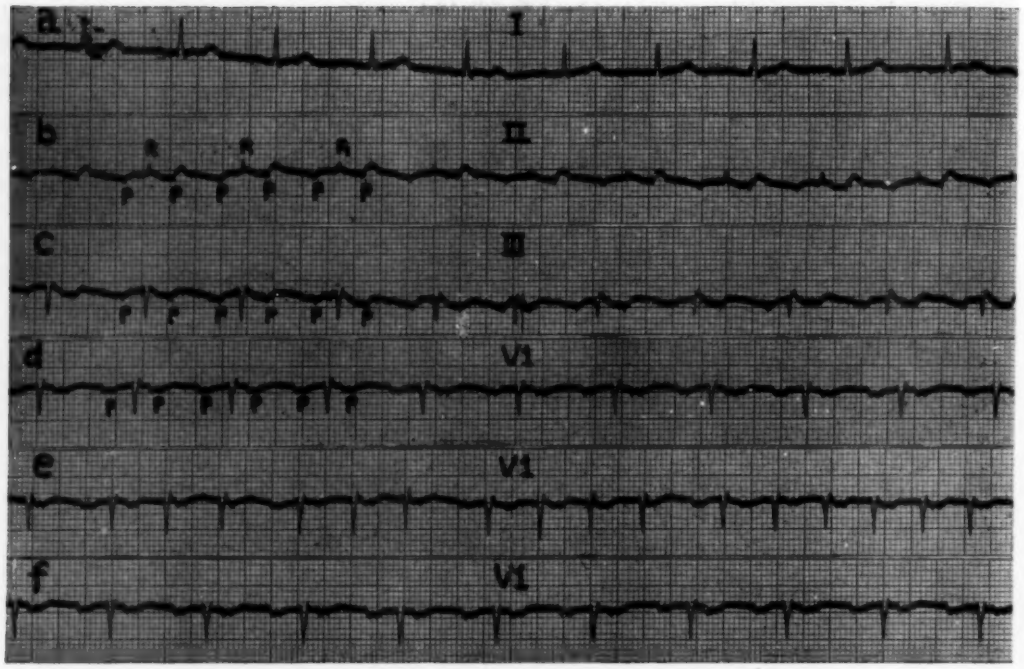

Fig. 2.—Effect of change from recumbency to sitting in paroxysmal atrial tachycardia with 2:1 A-V block: *a-d*, recumbent; *e*, immediately on attaining sitting position; *f*, recumbent after sitting.

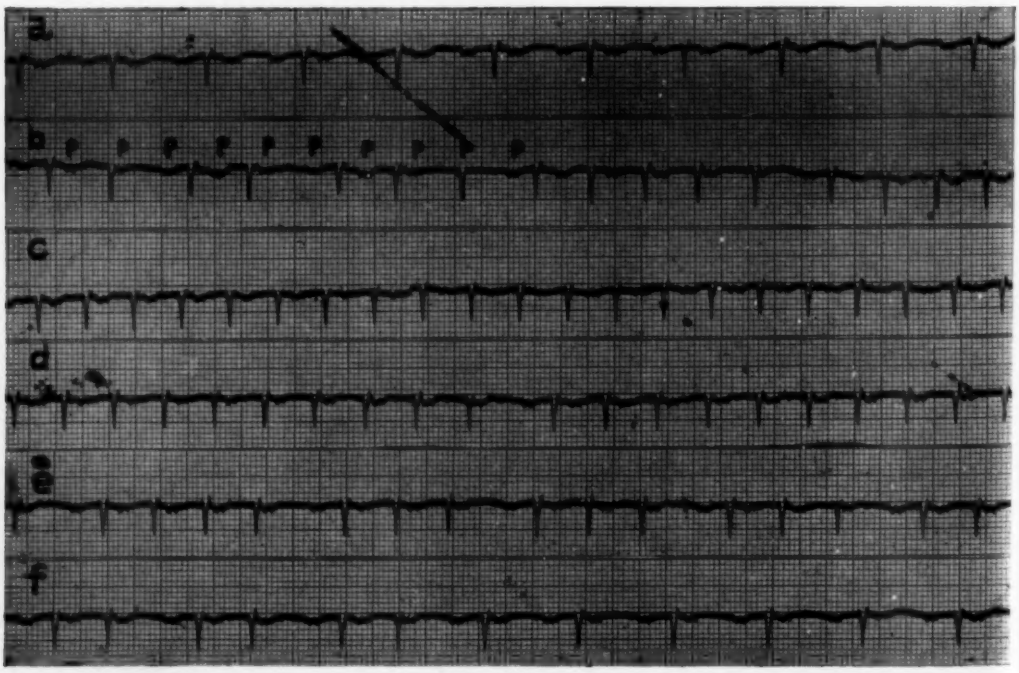

Fig. 3.—Effects of change from recumbency to sitting and of right carotid sinus pressure in paroxysmal atrial tachycardia with A-V block. Lead V_1: *a*, recumbent; *b*, immediately on attaining sitting position; *c* and *d* sitting position continued; *e*, continuous right carotid sinus pressure, subject sitting; *f*, on release of carotid sinus pressure, subject still sitting.

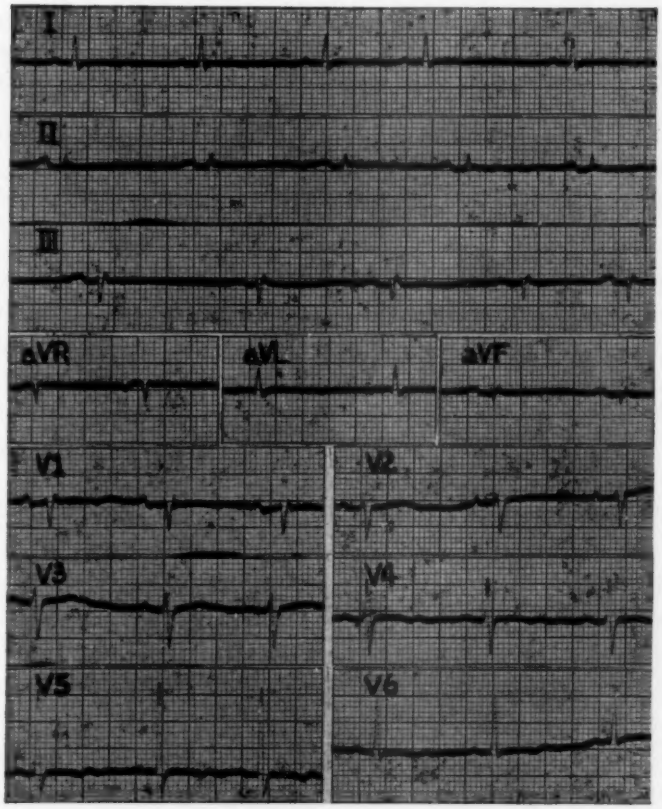

Fig. 4.—Sinus rhythm restored following 1.0 Gm. quinidine sulfate.

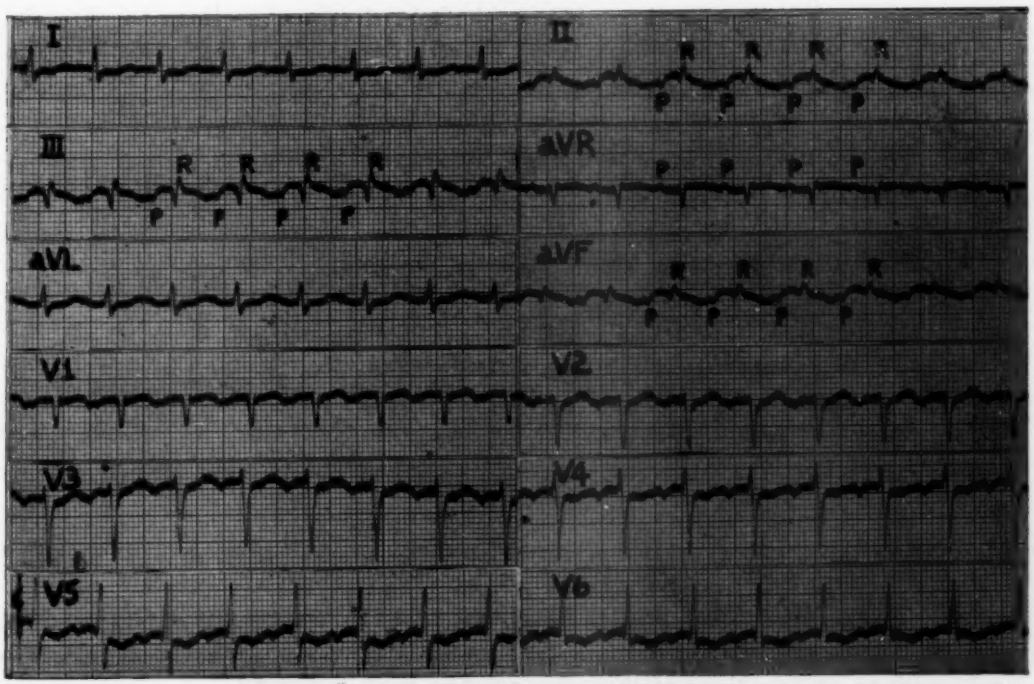

Fig. 5.—Paroxysmal atrial tachycardia without A-V block, rate 120 per minute, developing during intake of quinidine sulfate, 1.0 Gm. daily.

atrial tachycardia in which the atrial rate was 120 per minute and no A-V block was present in either the recumbent or sitting position (Fig. 5). The first of these was terminated by bed rest and a slight increase in quinidine dosage, while the second responded to 1.5 mg. of digitoxin given over a 36-hour period.

Three and one-half months following her initial digitalization the patient was still taking 0.15 mg. of digitoxin daily and had had no further episodes of tachycardia.

COMMENT

Heyl,[3] reporting originally the production by digitalis of paroxysmal atrial tachycardia with block, described the case of a 50-year-old man with hypertensive heart disease and pulmonary emphysema who in the recumbent position showed paroxysmal atrial tachycardia with a rate of 180 per minute and 2:1 A-V block; when this patient sat upright, his atrial rate fell to 150 per minute, but a 1:1 A-V ratio developed, causing an increase in ventricular rate from 90 to 150.

Geraudel[4] reported the case of a 63-year-old man with atrial tachycardia of long duration; the atrial rate in this subject ranged from 142 to 187, and A-V block varied in degree from time to time. Shift from a 2:1 to a 1:1 A-V ratio could be induced by lowering the subject's head, by changing him from the lying to the sitting position, and by shifting his position from one side to the other in bed. In this case the shift from a 2:1 to a 1:1 A-V ratio was abrupt, rather than gradual as in our case.

Fine and Miller[5] described the case of a 16-year-old girl, congenitally syphilitic, who gave a history of weakness, dizziness, and faintness on standing erect. She had a persistent atrial tachycardia with a rate varying from 136 to 200 standing and 108 to 180 sitting. Assumption of the recumbent position caused any one of three reactions: restoration of normal sinus rhythm; persistence of atrial tachycardia but at a slower rate; or the appearance of repeated short runs of atrial tachycardia separated by isolated sinus beats and showing incomplete A-V block and the Wenckebach phenomenon. The change in pulse rate in passing from the horizontal to the vertical position was instantaneous, while with shift back to the horizontal posture the rate change was sometimes abrupt and sometimes gradual.

Case 27 in the series of Decherd, Herrmann, and Schwab[6] was that of a 50-year-old Negro man with arteriosclerotic and hypertensive heart disease who had taken 3 grains of digitalis daily for 3 months. During recumbency this patient showed paroxysmal atrial tachycardia with 2:1 A-V block; carotid sinus pressure increased the block to 3:1 or 4:1. When the patient was allowed to sit upright, his heart rate doubled, and when he lay down again 2:1 A-V block was restored.

SUMMARY

1. A case of paroxysmal atrial tachycardia with A-V block, occurring in an elderly subject in the absence of digitalis administration, was presented.

2. Progressive shift from 2:1 A-V block to a 1:1 A-V ratio upon moving the subject from the recumbent to the sitting posture during a paroxysm was reported, and previous observations of this phenomenon were reviewed.

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Reports

STANDARDIZATION OF PHONOCARDIOGRAPHY

A Proposal Given at the Meeting Held in Stockholm Sept. 9, 1956, in Connection With the Second European Congress of Cardiology

IN PARIS in 1950 and 1953, two meetings on the standardization of phonocardiography were held, with Professor C. Lian presiding. The report of these meetings was published in this journal in 1955 (Am. Heart J. 50:82-84, 1955).

In the meantime, phonocardiography has been used more and more in medical and pediatric clinics, and its increasing value has been pointed out by many authors. Therefore, in connection with the Second European Congress of Cardiology, a third meeting on the same subject was held in Stockholm. Our aim now was to propose standardization based upon technical demands. At this meeting, Dr. Elmqvist read a short paper on some general technical considerations, followed by a discussion of a proposal on standardization written by Dr. Elmqvist and the chairman. Professor Lian emphasized the importance of the auditory curve. The following seven points of agreement were reached at the meeting. As these 16 doctors represent phonocardiographic experience from different countries of the world, I am convinced that the proposal will be of interest both to those who manufacture phonocardiographic apparatus and to those who use the method. These are the 7 points:

1. A phonocardiograph is an apparatus for recording mechanical vibration originating from the heart and adjacent vessels.

2. In order to get a record of the auscultative findings in accordance with the sensitivity of the human ear, means should be provided for recording according to the Fletcher O-isophon, i.e., the sensitivity of the apparatus should increase 14 db. per octave, by increasing frequency, from 15 to 600 cycles per second. Maximum allowed error is ±6 db. In the range from 600 to 800 cycles per second, the sensitivity may fall 6 db. This characteristic is called *auditory*.

3. In order to obtain further information from the frequency spectrum of the phonocardiogram, means may be provided for one or several additional frequency channels.

The channels employed should be named with the frequency at which the slope of the increase of sensitivity, by increasing frequency, is 15 db. per octave. The frequency which approximately is that at which the oscillations are recorded with the largest amplitude is called the nominal frequency of the channel.

The slope of the sensitivity curve should be outlined clearly in the description of the apparatus.

4. For further analysis it may be of value if more frequency channels are provided, whereupon an interval of about 1 octave between the standard frequencies is suitable.

5. The sensitivity should bear reference to the displacement of the unloaded chest wall, and the transmission from the thorax wall to the microphone should be taken into account.

6. Because of the transient nature of the heart sounds, it is important that transients originating from the filters be kept as small as possible. If a square electric potential is applied between the input terminals of the phonocardiograph, the developed transient should be decreased to 10 per cent of the initial deflection within 2 cycles.

7. The phonocardiograph may be provided with a device for determination of the constancy of sensitivity from microphone to graph.

EDGAR MANNHEIMER,* Chairman
Stockholm, Nov. 20, 1956

The participants were as follows:

Denmark:	E. Warburg	*Holland:*	D. H. Bekkering
			A. D. Erkelens
France:	C. Lian		J. W. Gerritsen
			J. Weber
Germany:	K. Holldack		H. Hartmann
	H. Maas		
	A. Weber	*U.S.A.*	H. B. Sprague
Great Britian:	A. Leatham	*Sweden:*	R. Elmqvist
	J. P. D. Mounsey		E. Mannheimer
			G. Ström

Dr. Holldack has informed the Chairman that he does not agree as far as Point 2 is concerned. He is not of the opinion that means should be made to get a record of the auscultative findings in accordance with the sensitivity of the human ear.

*Address Karolinska sjukhuset, Stockholm 60, Sweden.

STANDARDIZATION OF PHONOCARDIOGRAPHY: EFFORTS IN THE NETHERLANDS

D. H. Bekkering, and J. Weber*

The Hague, Holland

IN THE registration of heart sounds one has to consider the fact that the lower frequencies of the sounds show the highest intensities, while most of the information present in the sound is at the higher frequencies. From sheer necessity high-pass filters are used by manufacturers of phonocardiographs, with the result that heart sounds registered by various apparatus show quite different images. This variety in characteristics of phonocardiographs is one of the causes which hinder the exchange of phonocardiographic data.

To find a way out of these difficulties a Committee on Standardization of Phonocardiography was established by the National Health Research Organization T.N.O. By order of this Committee an apparatus has been developed at the Institute of Medical Physics T.N.O., by means of which it is possible to study the influence of the amplitude characteristic of the phonocardiograph on the phonocardiogram.

The apparatus consists of microphone, amplifier, tape recorder, repeating mechanism, filter unit with 60 high-pass filters (15 cutoff frequencies and 4 different slopes), auxiliary apparatus for the ECG and pulsation curves, and photographic recording unit.

It permits the registration of heart sounds with the ECG and a pulsation curve (carotid, ictus, or venae) on magnetic tape. A part of the magnetic tape, representing 2.5 sec. (2 to 3 heart cycles), can be selected and the signals on it are reproduced in a repeating manner. The sounds and reference curves are recorded, the sounds passing through the filter unit. By means of this method of repeating the sounds, it is possible to obtain a set of 60 phonocardiograms from the same heart cycle, permitting the study of the influence of filtering on such factors as the shape, onset, and termination of murmurs, and the visibility of the heart sounds, their duration, their splitting, etc.

Only the heart sounds of cases in which the diagnosis is established without the use of phonocardiographic arguments are used and recorded.

The series of phonocardiographs is referred for appraisal by cardiologists, members of the Committee on Standardization of Phonocardiography. An appraisal meeting starts with the case report; then, the criteria which are expected

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From the Institute of Medical Physics, National Health Research Council T.N.O., The Hague. Received for publication May 8, 1957.

*Now physicist of the Netherlands Institute for Preventive Medicine, Leyden.

to be found in the phonocardiogram are determined. Next, the series of phonocardiograms is examined and it is decided in which each criterion is most clearly visible; that is to say, which filters give the best pictures of the criterion in question.

Besides the judging of the filters, particular details in the phonocardiograms also are mentioned. At the same time phonocardiographic problems are discussed during the meetings.

With the above-mentioned method we intend to find out which filters for the different lesions most suit phonocardiographic work. We hope to learn how much shift in cutoff frequency and slope can be accepted without intolerable change in the phonocardiographic image.

As we have just started this work, it is still too early to give results, but our impression is that this method offers a good tool with which to study the influence of the filters. Already we presume to say that this influence is often very important.

Book Review

COLLAGEN DISEASES. By John H. Talbott, M.D., and R. Moleres Ferrandis, M.D., New York, 1956, Grune & Stratton, Inc., 232 pages, 30 illustrations.

This monograph is a well-written, comprehensive treatise on systemic lupus erythematosus, polyarteritis, dermatomyositis, systemic scleroderma, and thrombotic thrombocytopenic purpura. It represents many years of study, and each disease is clearly and thoroughly discussed in terms of historical survey, clinical variation, and recent concepts of pathogenesis. The cardiovascular manifestations in each condition are described and well documented.

With the apparent increase in the incidence of these diseases and the advances being made in the field of connective tissue, this book is recommended highly for its conciseness, clarity, and readability.

B.R.

Announcements

THE SEVENTH CONGRESS OF THE PAN-PACIFIC SURGICAL ASSOCIATION will be held in Honolulu, Hawaii, Nov. 14-22, 1957. All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons with sessions in all divisions of surgery and related fields promises to be of interest to all doctors.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Room 230, Young Building, Honolulu, Hawaii.

LIFE INSURANCE MEDICAL RESEARCH FUND: RESEARCH FELLOWSHIPS AND GRANTS. Applications for awards available July 1, 1958, will be received by the Life Insurance Medical Research Fund as follows: (1) Until Oct. 15, 1957, for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend is $3,800, with allowances for dependents and necessary travel. (2) Until Nov. 1, 1957, for grants to institutions in aid of research on cardiovascular problems. Support is available for physiologic, biochemical, and other basic work broadly related to cardiovascular problems, as well as for clinical research in this field. Approximately $1,000,000 will be available for the two types of award. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.